Advances in Life Science and Technology
ISSN 2224-7181 (Paper) ISSN 2225-062X (Online)
Vol.44, 2016

Bee Venom and Its Therapeutic Values: A Review

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Abstract
Apitherapy is the medicinal therapeutic use of honeybee products, consisting of honey, propolis, royal jelly, pollen, beeswax and, in particular, bee venom. The aims of this paper were to review bee venom and its therapeutic values. Bee venom therapy is the therapy which utilizes the application of bee venom to treat various diseases and it has been used since ancient times in traditional medicine. Bee venom is produced by the venom gland located in the abdominal cavity and contains several biologically active peptides, including melittin (a major component of BV), apamin, adolapin, mast cell degranulating peptide, and enzymes (phospholipase A2, and hyaluronidase) as well as non-peptide components, such as histamine, dopamine, and norepinephrine. Bee venom has therapeutic values against variety of disease like Arthritis, nervous system diseases, heart and blood System abnormalities and for skin disease. Furthermore, Bee venom has been widely used in the treatment of some immune-related diseases, as well as in recent times in treatment of tumors. Several cancer cells, including renal, lung, liver, prostate, bladder, and mammary cancer cells as well as leukemia cells, can be targets of bee venom peptides such as melittin and phospholipase A2. In order to benefit from the promising role of bee venom therapy research should be extended to identify their specific component and target action.
Keywords: Apitherapy, anticancer, bee venom, bee, melittin

1 INTRODUCTION

Use of honey and other bee products can be also traced back thousands of years and healing properties are included in many religious texts including the Veda, Bible and Quran (Lee et al., 2005; Adewole et al., 2015). Apitherapy is the medicinal therapeutic use of honeybee products, consisting of honey, propolis, royal jelly, pollen, beeswax and, in particular, bee venom (BV) (Lee et al., 2005; Ali, 2012). Bee venom (BV) therapy which utilizes the application of bee venom to treat various diseases has been used since ancient times in traditional medicine (Liu and Tong, 2003; Lee et al., 2005; Ali, 2012; Silva et al., 2015). It is based on the fact that these crude extracts exhibit a wide variety of pharmacologically active molecules. This pool of chemical compounds is formed by biogenic amine, enzymes (phospholipase A2), basic peptides and proteins (melittin and apamin) and a mixture of water-soluble and nitrogen-containing substances (Santos et al., 2011; Silva et al., 2015).

Bee venom contains a variety of different peptides, including melittin, phospholipase A2, apamin, adolapin, and mast cell-degranulating peptide (MCDP) (Kwon et al., 2002; Park et al., 2004). Among these compounds, melittin, a small linear peptide consisting of 26 amino acids, is the major component of bee venom (Wang et al., 2009). Depending on the disease being treated, BV therapy can be used by applying a cream, liniment, or ointment, via injection, acupuncture or even directly through a live bee sting (Ali, 2012). The most commonly used method is bee venom acupuncture (BVA), which involves the injection of diluted bee venom into acupuncture points. It can be employed as an alternative medicine in patients with PD, pain and other inflammatory diseases, such as rheumatoid arthritis and osteoarthritis (Lee et al., 2005; kim and Jeon, 2014).
Bee venom has been used as a traditional medicine to treat back pain, rheumatism, and skin diseases by its antibacterial, antiviral, and anti-inflammatory effects (Park et al., 2010; Wang et al., 2009). Moreover, several studies have demonstrated that bee venom and/or melittin have anti-cancer effects including prostate, liver, breast, cervical, renal (Park et al., 2010a) cancer cells. Interestingly, BV has also been used in humans to treat neurological diseases with neuroinflammatory aspects, such as multiple sclerosis and Parkinson's Disease (Park et al., 2010; kim and Jeon, 2014)

Currently, several treatments for disease like cancer are very costly and have numerous side effects. Due to this anticancer drug developments from natural resources are ventured throughout the world. Venoms of several animal species including bee have shown promising therapeutic potential against cancer. Therefore, the objective of this paper is to review recent article regarding bee venom and its therapeutic values.

2 Properties and Composition of Bee Venom

Honeybee venom is a transparent liquid dries up easily even at room temperature, odourless, ornamental pungent smell, a bitter taste, hydrolytic blend of proteins with basic pH (4.5 to 5.5) that is used by bees for defense. When coming into contact with mucous membranes or eyes, bee venom causes considerable burning and irritation. Bee venom is soluble in water and insoluble in alcohol and ammonium sulfate. When it comes in contact with air it forms grayish-white crystals. Dried venom takes on a light yellow colour and some commercial preparations are brown, thought to be due to oxidation of some of the venom proteins. Bee venom

contains a number of very volatile compounds which are easily lost during collection, it is considered a rich source of enzymes, peptides and biogenic amines, it is specific weight 1.1331 (Ali, 2012). The bee venom contains 88% water. The glucose, fructose and phospholipid contents of venom are similar to those in bee's blood (Bogdanov, 2015)

Bee venom is a complex mixture of proteins, peptides and low molecular components. Nowadays its components have been characterized. The main components are proteins and peptides. The composition of fresh and dried BV differs mainly in regards to the volatile components; the overall biological activity is similar (Zolfagharian et al., 2015; Bogdanov, 2015).

2.1 Polypeptides

Bee venom contains a variety of peptides, including melittin, apamin, adolapin, the mast-cell-degranulating peptide, enzymes (phospholipase A2) biologically active amines (i.e. histamine, epinephrine), and a non peptide components with pharmaceutical properties (Roy et al., 2015). Polypeptides are smaller in molecular weight than enzymes, made of 2 or more amino acids. BV has numerous polypeptides, the main one being melittin, which is also the main component of BV. Melittin has a MW of 2840 daltons but it can reach 12500 daltons because it can be also in a tetrameri form (Bogdanov, 2015).

Peptide is a potent anti-inflammatory agent; however, at low concentration it is a strong mediator of mast cell degranulation and histamine release from mast cells, which are present in the blood supply and in all tissues perfused by blood. (Ziai, 1990; Moreno and Giralt, 2015) Bradykinin is a physiologically active peptide that belongs to the kinin group of proteins. Bradykinin and related kinins act on two receptors, designated as B1 and B2. The former is expressed only as a result of tissue injury and it is thought to play a role in chronic pain. In contrast, the B2 receptor is constitutively expressed, participating in vasodilatation via the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor, thus contributing to lowering blood pressure (Sharma, 2014). Adolapin is a peptide that was first isolated from bee venom in the 80s. It exerts a potent analgesic effect and anti-inflammatory activity in rats, blocking prostaglandin (Moreno and Giralt, 2015)

2.2 Enzymes

When focusing on enzymes related to toxicity, phospholipase and hyaluronidase are the two major enzymatic proteins present in hymenoptera venom. These enzymes can trigger an immune response, inducing IgE response in susceptible individuals (Cichocka, 2012). Phospholipase A2 (PLA2) is a calcium-dependent enzyme that hydrolyzes the sn-2 ester of glycerophospholipids to produce a fatty acid and a lysophospholipid. It destroys phospholipids, disrupting the integrity of the lipid bilayers, thus making cells susceptible to further degradation. In fact, PLA2 reaction products, such as lysophosphatidylcholine, lysophosphatidic acid and sphingosine 1-phosphate, can have cytotoxic or immunostimulatory effect on diverse cell types, causing inflammation and immune responses (Gräler, 2012).

Hyaluronidase is commonly known as a “spreading factor” because it hydrolyzes the viscous polymer hyaluronic acid into non-viscous fragments. When extracellular matrix is destroyed by hyaluronidase, the gaps between cells facilitate the invasion of venom toxins. Therefore, venom penetrates tissues and enters blood vessels, thus catalysing systemic poisoning. Furthermore, hydrolyzed hyaluronan fragments are pro-inflammatory, pro-angiogenic and immunostimulatory, thus inducing faster systemic envenomation Girish, 2007).

2.3 Low molecular compounds

BV contains smaller quantities of low molecular compounds are different in nature: amino acids, catecholamines, sugars and minerals (Zolfagharian et al., 2015; Bogdanov, 2015). These small molecules are minerals, amino acids, and physiologically active amines, such as catecholamines. Among this category, histamine is one of the major components. This organic nitrogenous compound participates in the inflammatory response by increasing the permeability of capillaries. In a similar manner, the catecholamines dopamine and nor-adrenaline increase heartbeat, thereby enhancing venom circulation and thus, its distribution. However, like histamine, the effects of these two catecholamines are largely overshadowed by those of other components of venom. Serotonin can act as an irritant and can contribute to the pain caused by the venom. Finally, high levels of acetylcholine are detected only in wasp venom. Acetylcholine can increase perceived pain of a sting by stimulating pain receptors synergically with histamine effects (Moreno and Giralt, 2015).

3 THERAPEUTIC VALUES OF BEE VENOM

BV is a well-known pharmacologically active product of the hive synthesized by the venom glands associated with the sting apparatus of worker and queens, stored in the venom reservoir, and injected through the sting apparatus during the stinging process (Schmidt and Buchmann, 1999). Due to its anti-oxidants, anti-coagulants, anti-inflammatory properties and bioactive substances like melittin and phospholipase BV mainly used to treat

many inflammatory disorders such as arthritis, cancer, diseases of nerveous system, heart and blood system abnormalities, skin diseases and others (Castro *et al*., 2005). Furthermore, therapeutic application of bee venom include their use in the management of bursitis, tendonitis, dissolving scar tissue, in the management of post-herpetic neuralgia, Lyme disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis, TMDs and more (Ram et al., 2014).

3.1 BV Against Arthritis

Bee venom(BV) uses in treating arthritis by blocking the building of the pro inflammarory substances *c*ytokinine, PGE-2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2, and inhibiting the proliferation of rheumatoid synovial cells (Krylov *et al.,* 2007). After applying different methods of venom administration like: bee stings, api-puncture, injections, electrophoresis and application with ultrasound waves (phonophoresis); good success rates lying between 60 and 90 % have been achieved (Son *et al.,* 2007). In last 10 years api-puncture has been developed as a new technique for treating arthritis (Urtubey, 2005). Additionally, bee venom does not influence rheumatoid deformation, as shown by patients X-rays, but it acts by controlling pain and inflammation (Krylov *et al.,* 2007). Furthermore, BV also use in the treatment of different pain conditions: Neck pain, low back pain, herniated lumbar pain, and disc pain, shoulder pain after stroke, acute ankle sprain, wrist sprain, rheumatoid arthritis and knee osteoarthritis while bee sting(BS) and api-puncture (AP) therapy are proved to be useful in all these conditions (Lee *et al.,* 2005). Researchers claim that bee venom therapy is better than hormone therapy; as hormone therapy causes unfavorable side effects such as the reduction in the activity of these vital hormone glands, while the BV constantly activates the activity of hormonal systems (Bogdanov, 2015)

3.2 BV Against Cancer

BV has anti-cancer activities, due mainly to two substances that have been isolated and characterized: melittin and phospholipase A_2 (PLA_2). Although melittin and PLA_2 are the two major components in the venom of the species *Apis mellifera* and many studies have describing their antitumoral effects (Ownby et al., 1997). BV acts against different types of cancer in cell as melittin; a powerful anticancer peptide might be the better choice than whole BV (Orsolic, 2005). Melittin is multifuctorial ingredient in BV that diminishes surface tension of membranes and stabilises them, exerts anti-inflammatory activity in very small doses, stimulates smooth muscles, activates the hypophysis and adrenal glands; increases capillary permeability increasing blood circulation and lowering the blood pressure, lowers blood coagulation, immunostimulatory and immunosuppressive, radiation protective, influences the central nervous system,anticancer (Bogdanov, 2015). On the other hand, bee venom acupuncture and melittin were used to control neuropathy caused by cancer chemotherapy (Park, 2010). Moreover, bee venom peptide lasioglossin II exhibits cytotoxic activity against various cancer cells in vitro (Park *et al.,* 2012; Bandyopadhyay *et al.,* 2013).

3.3 BV Against Nervous System Diseases

BV has different effects on the central and peripheral nervous system and used for the treatment of different neurological conditions such as Multiple Sclerosis (MS), amyotropic lateral sclerosis (ALS) Alzheimers and Parkinson (Hwang *et al*, 2015). Changes in Glutamate, the predominant excitatory neurotransmitter in the central nervous system, alters the activity of glutamate transporters in many neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Hauser *et al.,* 2001). But BV is helpful in reducing glutamatergic cell toxicity in neurodegenerative diseases as it protects cell death and significantly inhibits the cellular toxicity of glutamate, and pretreatment with BV altered MAP kinase activation following exposure to glutamate (Lee *et al.,* 2011).

3.4 Therapeutic Effects of BV on Heart and Blood System Abnormalities

BV increases coronary and peripheral blood circulation, improves the blood microcirculation ,slows down heart at lower doses and stimulates it at higher ones, lowers blood pressure, antiarhythmic against blood coagulation and fibrinolytic, stimulates the building of erythrocytes (Savilov, 2010). It also uses in alleviations of hypertension, arteriosclerosis, endarteritis (chronic inflammation of the inner layer of arteries) angina pectoris arrhythmia (Krylov *et al.,* 2007).

3.5 Therapeutic Effects of BV Againt Skin Disease

Researchers claimed that BV has therapeutic effects against many skin diseases like eczema, dermatitis, psoriasis furunculosis (recurring boil)**,** cicatrices**,** baldness, acne and other diseses (Kim *et al.,* 2015) other disease such as: opthamology**,** gastroentorology: colitis, ulcers, pulmonology: asthma, bronchitis, otorinolaringology: pharingytis, tonsillitis, ear nerveneuritis**,** endocrinology, urology, gynecology (Hegazi *et al.,* 2012).

4 Conclusion

Apitherapy is the use of honey bee products for medical purposes whereas; bee venom therapy is the use of live bee stings (or injectable venom) to treat various diseases. Bee venom is a complex mixture of proteins, peptides and low molecular components. The main components are proteins and peptides. Therapeutic application of bee venom include their use in the management of bursitis, tendonitis, dissolving scar tissue, in the management of post-herpetic neuralgia, Lyme disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis, TMDs and more. In order to benefit from the promising role of bee venom therapy research should be extended to identify their specific component and target action. Although, bee venom is safe for human treatment; it should only be used under the supervision of a qualified health care professional.

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