Review Article

Therapeutic effects of bee venom

Running Title: Bee Venom

Abstract:

Bee venom (BV) has a long history of use in Korea for the relief of pain symptoms and for the treatment of various inflammatory diseases, including rheumatoid arthritis. There is some evidence for the underlying mechanisms involved in the venom's anti-inflammatory and analgesic activities. Recent clinical and experimental reearch has confirmed that the venom and its active components can be applied to a broad spectrum of immunological and neurodegenerative diseases, including autoimmune diseases and Parkinson's disease. BV has been shown to exhibit these effects by modulating immune cells in the periphery, together with glial cells and neurons in the central nervous system. This review sets out the latest scientific evidence concerning the therapeutic effects of BV and various components thereof in the context of a number of diseases, and provides a detailed description of the mechanisms.

Key words: Bee venom, allergic disorders, cancer

Introduction

Bee venom (BV) therapy is a traditional form of medicine dating back to ancient Greece and China. Scientific reports describing the venom's anti-rheumatic and anti-inflammatory properties have appeared for at least a century.[1] BV is traditionally employed for analgesic purposes and to treat back pain, rheumatism, and skin diseases by its antibacterial, antiviral, and anti-inflammatory effects.[2,3] The product may be administered systemically or by means of chemical stimulation of acupoints, a therapy known as "BV acupuncture" or "apipuncture". BV contains a wide range of active components, including melittin, phospholipase A2, apamin, adolapin, and mast cell-degranulating peptide (MCDP).[4,5] Recent research has also hypothesized that BV and the active components derived from it may exhibit powerful ameliorative effects on refractory immunological and neurodegenerative conditions, including

multiple sclerosis and Parkinson's Disease.[2,6] This review discusses the ameliorative effects and mechanisms of BV-derived active components, particularly PLA2, melittin and apamin.

Therapeutic Effects of BV on Allergic Disorders:

The onset of allergic disorders, such as asthma, allergic rhinoconjunctivitis, and atopic eczema, is triggered by the production of allergen-specific $CD4^+$ T cells.[7] From a general perspective, allergy is a disease mediated by T helper 2 (Th2) cells characterized by overproduction of specific immunoglobulin E (IgE) antibodies. Interleukin-4 (IL-4) and IL-13, the key Th2-specific cytokines, make a particular contribution to these.[8]

BV therapy is a form of allergen-specific immunotherapy (SIT) with a long history. Although the mechanism involved in SIT is still largely unclear, a number of essential features have been identified. These include modifications of antigen presenting cells (APCs), T cells, and B cells, and changes in the numbers and the functions of effector cells responsible for allergic response mediation.[9] Clinical trials have confirmed that SIT enhances the production of IL-10 by APCs, including B cells, monocytes, and macrophages.[9] The therapy has also been shown to be particularly efficacious in insect venom and respiratory allergies. BV immunotherapy exhibits early- and late-stage effects on the principal cells involved in allergic inflammation.[7] Venom immunotherapy triggers monocyte activation in which overproduction of IL-12 and tumor necrosis factor alpha (TNF-α), cytokines linked to Th2 cell suppression is delayed.[10] The principal allergen in BV is PLA_2, known to be capable of triggering leukotriene C4 production from purified human basophils in as short a period as 5 min, while IL-4 is expressed and produced subsequently with no histamine release.[11] One study reported that direct injection of the BV-derived PLA_2 ($bvPLA_2$) into the inguinal lymph nodes resulted in improved allergen-specific IgG and T-cell responses.[12]

Melittin (MEL) is a major BV peptide constituent regarding as being of potential benefit in the treatment of cancer. Recent studies have implicated a number of mechanisms of MEL cytotoxicity in various types of cancer cells. These include the effect of cell cycle changes on proliferation and/or growth inhibition, and the triggering of apoptotic and necrotic cell death via various cancer cell death mechanisms, including the activation of caspases and matrix metalloproteinases. While the peptide is cytotoxic to a wide range of tumor cells, it is also toxic to normal cells. If full therapeutic benefit is therefore to be obtained, an appropriate means of delivery is essential. This could involve MEL nanoparticles capable of safely delivering significant quantities of MEL via the intravenous route, and of targeting and destroying tumors.[13]

Therapeutic Effects of BV on Autoimmune and Inflammatory Diseases:

Autoimmune diseases, a group including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, were previously regarded as Th1-dominant conditions.[1] However, Th17 cells and Tregs have also recently been observed to play a major role in autoimmune diseases.[14] BV has been used in traditional medicine to treat chronic inflammatory diseases, including arthritis by blocking the building of the pro inflammarory substances cytokinine, PGE-2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2, and inhibiting the proliferation of rheumatoid synovial cells.[15] The anti-rheumatic and anti-inflammatory effects of BV have been known for at least a century.[1] In their rat study, Kwon et al. showed that BV injection into the Zusanli acupoint elicited anti-inflammatory and anti-nociceptive effects on Freund's adjuvant-induced arthritis.[16] Combined BV therapy and medication has been reported to be superior to the use of medication alone in improving the symptoms of rheumatoid arthritis. This combined therapy might also reduce the high doses of Western medicines that are currently being employed.[17] These anti-arthritic benefits have been described in various arthritis models. These effects of BV may be associated with melittin, a major peptide component of the venom, with well-established anti-inflammatory and anti-arthritis properties, and suppressive effects on nuclear factor kappaB (NF-κB).[13]

Lupus nephritis, a particularly severe complication of systemic lupus erythematosus, results from glomerular inflammation associated with the production of autoantibodies against the nucleus and of cytokines/chemokines, and eventually leads to irreversible kidney injury.[18] Foster reported the age-dependent development of autoimmune disease in female New Zealand Black/White F1 mice, characterized by glomerulonephritis, proteinuria, and renal dysfunction.[19]

Multiple sclerosis is a chronic inflammatory disease affecting the central nervous system (CNS), with more than a million sufferers across the world. Clinical manifestations include ataxia, loss of coordination, sensory and cognitive dysfunction, and fatigue.[20] The pathogenesis is known to involve autoimmune T cell responses, in which Th1 and Th17 cells play critical roles.[21]

Therapeutic Effects of BV on Neurological Diseases:

Parkinson's disease (PD) is a particularly common progressive neurodegenerative disorder, the clinical manifestations of which include bradykinesia, resting tremor, rigidity, and posture and gait impairment deriving from selective and irreversible dopaminergic (DA) neuron losses in the substantia nigra and of their terminals in the striatum.[22] Activated microglia,

consisting of innate immune cells in the central nervous system, in close proximity to degenerating DA neurons have been identified as a key mediator of neuroinflammation in PD.[22]

Therapeutic Effects of BV on Heart and Blood System Abnormalities:

BV increases coronary and peripheral blood circulation, improves the blood microcirculation, lowers blood pressure, stimulates the building of erythrocytes.[23] It also uses in alleviations of hypertension, arteriosclerosis, endarteritis, angina pectoris arrhythmia.[15]

Therapeutic Effects of BV Againt Skin Disease:

BV has therapeutic effects against eczema, dermatitis, psoriasis furunculosis (recurring boil), cicatrices, baldness, acne and other diseses.[24] It also uses in alleviations of opthamology, colitis, ulcers, asthma, bronchitis, pharingytis, tonsillitis, ear nerveneuritis.[25]

Therapeutic Effects of BV Against Cancer:

BV has anti-cancer activities due mainly to two substances such as melittin and phospholipase A2 (PLA2). BV acts against different types of cancer in cell as melittin, a powerful anticancer peptide.[26] Melittin is 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.[27]

Conclusion:

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, amino acids, catecholamines, sugars and minerals.[27] The existing evidence indicates that BV has therapeutic effects against allergic, autoimmune, inflammatory, neurological, skin, cancer, heart and blood system abnormalities disorders. Future studies including detailed experimental investigation of cellular and molecular mechanisms, together with well-controlled, randomized clinical trials, may eventually yield a therapeutic alternative in the treatment of various disorders.

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