

3 **Therapeutic effects of bee venom**

4
5 **Running Title:** Bee Venom

6
7 **Abstract:**

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

18 **Key words:** Bee venom, allergic disorders, cancer

19 **Introduction**

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

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

32 **Therapeutic Effects of BV on Allergic Disorders:**

33 The onset of allergic disorders, such as asthma, allergic rhinoconjunctivitis, and atopic
34 eczema, is triggered by the production of allergen-specific CD4⁺ T cells.⁷ From a general
35 perspective, allergy is a disease mediated by T helper 2 (Th2) cells characterized by
36 overproduction of specific immunoglobulin E (IgE) antibodies. Interleukin-4 (IL-4) and IL-
37 13, the key Th2-specific cytokines, make a particular contribution to these.⁸

38 BV therapy is a form of allergen-specific immunotherapy (SIT) with a long history. Although
39 the mechanism involved in SIT is still largely unclear, a number of essential features have
40 been identified. These include modifications of antigen presenting cells (APCs), T cells, and
41 B cells, and changes in the numbers and the functions of effector cells responsible for allergic
42 response mediation.⁹ Clinical trials have confirmed that SIT enhances the production of IL-10
43 by APCs, including B cells, monocytes, and macrophages.⁹ The therapy has also been shown
44 to be particularly efficacious in insect venom and respiratory allergies. BV immunotherapy
45 exhibits early- and late-stage effects on the principal cells involved in allergic inflammation.⁷
46 Venom immunotherapy triggers monocyte activation in which overproduction of IL-12 and
47 tumor necrosis factor alpha (TNF- α), cytokines linked to Th2 cell suppression is delayed.¹⁰
48 The principal allergen in BV is PLA₂, known to be capable of triggering leukotriene C4
49 production from purified human basophils in as short a period as 5 min, while IL-4 is
50 expressed and produced subsequently with no histamine release.¹¹ One study reported that
51 direct injection of the BV-derived PLA₂ (bvPLA₂) into the inguinal lymph nodes resulted in
52 improved allergen-specific IgG and T-cell responses.¹²

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

63 **Therapeutic Effects of BV on Autoimmune and Inflammatory Diseases:**

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

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

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

91 **Therapeutic Effects of BV on Neurological Diseases:**

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

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

99 **Therapeutic Effects of BV on Heart and Blood System Abnormalities:**

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

103 **Therapeutic Effects of BV Against Skin Disease:**

104 BV has therapeutic effects against eczema, dermatitis, psoriasis furunculosis (recurring boil),
105 cicatrices, baldness, acne and other diseases.²⁴ It also uses in alleviations of ophthalmology,
106 colitis, ulcers, asthma, bronchitis, pharyngitis, tonsillitis, ear nerveneuritis.²⁵

107 **Therapeutic Effects of BV Against Cancer:**

108 BV has anti-cancer activities due mainly to two substances such as melittin and phospholipase
109 A2 (PLA2). BV acts against different types of cancer in cell as melittin, a powerful anticancer
110 peptide.²⁶ Melittin is diminishes surface tension of membranes and stabilises them, exerts anti-
111 inflammatory activity in very small doses, stimulates smooth muscles, activates the
112 hypophysis and adrenal glands; increases capillary permeability increasing blood circulation
113 and lowering the blood pressure, lowers blood coagulation, immunostimulatory and
114 immunosuppressive, radiation protective, influences the central nervous system, anticancer.²⁷

115 **Conclusion:**

116 Bee venom therapy is the use of live bee stings (or injectable venom) to treat various diseases.
117 Bee venom is a complex mixture of proteins, peptides, amino acids, catecholamines, sugars
118 and minerals.²⁷ The existing evidence indicates that BV has therapeutic effects against
119 allergic, autoimmune, inflammatory, neurological, skin, cancer, heart and blood system
120 abnormalities disorders. Future studies including detailed experimental investigation of
121 cellular and molecular mechanisms, together with well-controlled, randomized clinical trials,
122 may eventually yield a therapeutic alternative in the treatment of various disorders.

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