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Review article

Bee venom for the treatment of Parkinson's disease: How far is it possible?

Kamal Awad[a,b,1], Abdelrahman Ibrahim Abushouk[a,c,d,1], Ahmed Helal AbdelKarim[a,b], Maged Mohammed[a,b], Ahmed Negida[a,b,*], Ali S. Shalash[e]

[a] Medical Research Group of Egypt, Cairo, Egypt
[b] Faculty of Medicine, Zagazig University, Zagazig, Egypt
[c] Faculty of Medicine, Ain Shams University, Cairo, Egypt
[d] NovaMed Medical Research Association, Cairo, Egypt
[e] Neurology Department, Ain Shams University, Cairo, Egypt

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta leading to depletion of striatal dopamine and motor symptoms as bradykinesia, resting tremors, rigidity, and postural instability. Current therapeutic strategies for PD are mainly symptomatic and may cause motor complications, such as motor fluctuations and dyskinesia. Therefore, alternative medicine may offer an effective adjuvant treatment for PD. Bee venom therapy (BVT) has long been used as a traditional therapy for several conditions, such as rheumatoid arthritis, asthma, and skin diseases. Experimental and clinical studies showed that BVT could be an effective adjuvant treatment for PD. Several mechanisms were suggested for these findings including the ability of BVT to attenuate neuroinflammation, inhibit apoptosis of dopaminergic neurons, protect against glutamate-induced neurotoxicity, and restore normal dopamine levels in the nigrostriatal pathway. In this article, we reviewed and summarized the literature regarding the potential of BVT for the treatment of PD.

Contents

Abbreviations: BV, bee venom; BVA, bee venom acupuncture; BVT, bee venom therapy; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; PD, Parkinson's disease; SN, substantia Nigra; UPDRS, United Parkinson's Disease Rating Scale.

* Corresponding author at: Faculty of Medicine, Zagazig University, 44519, Zagazig, Egypt.
E-mail addresses: ahmed01251@medicine.zu.edu.eg, dr.negida@gmail.com (A. Negida).

[1] These authors contributed equally to this work.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD) [1–3], with a growing prevalence that reaches up to 3% in the population over 80 years [4]. Clinically, PD is characterized by cardinal motor symptoms, such as bradykinesia, resting tremors, rigidity, and postural instability [5], in addition to non-motor symptoms that include neuropsychiatric symptoms, sleep disorders, dysautonomia, gastrointestinal symptoms, and sensory complaints [6].

Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and deposition of ubiquinated misfolded proteins, known as Lewy bodies, in the cytoplasm of neurons [4,7–9]. The exact pathogenic mechanisms that cause the selective damage of dopaminergic neurons in PD patients are not completely understood. However, the current literature suggests that oxidative stress, neuroinflammation, mitochondrial dysfunction, and altered protein handling play a key role in the pathogenesis of PD [9–12].

Current treatment options for PD are mainly symptomatic and remain focused on motor symptoms only [13,14]. PD treatment targets normalizing the activity and chemical composition of the basal ganglia by restoring striatal dopamine levels [13]. Currently, L-dopa, a dopamine precursor, is one of the most effective drugs for PD [13,15]. However, after five years of levodopa treatment, about 50% of PD patients develop treatment-related complications, such as levodopa induced dyskinesia, motor fluctuations, hallucinations, and somnia [15–20]. Due to these limitations, investigators are searching for new therapeutic strategies for PD. There is an unmet need to find neuroprotective agents to slow the progress of PD and adjuvant drugs to decrease the need for levodopa and overcome its treatment-related complications [21].

Bee venom therapy (BVT) is a widespread alternative therapy that originated from the ancient China and Greece [22]. It contains many active substances (e.g. peptides, enzymes, and biogenic amines) with different pharmacological actions [22,23]. Although BV can cause neurotoxic and nociceptive effects, it also has anti-inflammatory [24,25], anti-nociceptive [26], radioprotective [27], and anti-mutagenic [28,29] effects. Therefore, it has been used as a traditional therapy for several diseases, such as rheumatoid arthritis, asthma, cancer, and skin diseases [30–32]. There are various methods to administer BVT: it can be applied as a cream, ointment, liniment, injection, acupuncture, or directly through a living bee [13,33]. However, bee venom acupuncture (BVA) is considered the most common mode of administration [13]. In terms of safety, no toxic effects of BV were noted when it was used at supratherapeutic levels (100 to 200 folds) [13,34].

Mellitin, a 26 aminoacid peptide, is the primary component of BV (40% to 60%) [35]. At high doses, it causes severe local pain and inflammation, while in lower doses, it can increase capillary permeability, exert anti-inflammaory effects, and lower blood pressure [36]. Since the early 1970s, studies have shown that mellitin can disrupt the brain's bioelectrical activity and inhibit the general behavior in animal models [22,37]. Moreover, it has been proven to inhibit apoptosis in SH-SY5Y cells and mitigate the inflammatory response of microglial cells [38].

Another component of BV is apamin (2% of BV content), an 18 aminoacid peptide, that is widely recognized as an irreversible blocker of Ca+ activated K+ channels [35,39]. These channels are responsible for neuronal hyperpolarization and are found mainly in AMPA and NMDA glutamatergic synapses [40]. Therefore, blocking these channels can reduce hyperpolarizing effects, enhance synaptic plasticity and memory functions [41,42]. Moreover, BV contains phospholipase A2 (PLA2), an enzyme that catalyzes the hydrolysis of membrane phospholipids, plays a vital role in signal transduction and regulates inflammatory responses [43].

Several studies showed the therapeutic potential of BV in multiple neurological diseases. In rat and mice models of multiple sclerosis, BV treatment was shown able to increase the count of T-regulator cells and suppress pro-inflammatory cytokine production; therefore, attenuating experimental autoimmune or allergic encephalomyelitis [44]. Moreover, in mutant superoxide dismutase-1 ($hSOD1^{G93A}$) transgenic mice, serving as models for amyotrophic lateral sclerosis (ALS), subcutaneous BV acupuncture (at a dose of 0.1 μg/g—three times/week for two weeks) improved the mice motor activity on the rotarod test and increased the lifespan of treated mice [45,46]. In AD mice models, treatment by BV-PLA2 improved cognitive functions and cerebral glucose metabolism and reduced the levels of hippocampal amyloid-Beta deposits [47].

Recently, multiple experimental studies have investigated the anti-neuroinflammatory effects of BVT as a possible treatment for PD, and interestingly, these studies showed promising results. In this article, we aimed at summarizing and reviewing the literature regarding the potential use of BVT for the treatment of PD.

2. Mechansims of action of bee venom in Parkinson's disease

2.1. Attenuation of neuroinflammation and microglial activation

Abnormal microglial activation is a pathological hallmark in neurodegenerative diseases, including PD and AD [48]. Experimental activation of BV2 microglial cells (brain microglial cells from C57BL/6 mice), using bacterial lipopolysaccharide (LPS), increases the expression of tumor necrosis factor (TNF-α) and inducible nitric oxide synthase (iNOS), promoting neuroinflammation and nitric oxide (NO)-mediated neuronal death [49]. Moreover, activated microglia can generate superoxide free radicals via activation of NADPH oxidase enzyme [50,51]. It is also believed that activated microglia play a role in dopaminergic terminal loss in early PD [52].

Several preclinical trials examined whether BV can attenuate leukocyte migration or microglial activation in cellular and animal models. Moon et al. reported the ability of BV and its peptide (mellitin) to inhibit the expression of NO and iNOS in LPS-stimulated BV2 microglia in a dose-dependent manner [53]. Yang et al. showed that pretreatment of mutant hSOD1 transgenic mice (serving as an animal model for ALS) suppressed the expression of microglial markers in the brain stem and spinal cord [45]. Moreover, Jang et al. suggested that BV can prevent microglial activation and leucocyte migration through its antibacterial effect, removing a possible source of microglial stimulation [54]. In another animal study by Chung et al., BV reduced brain tissue infiltration with CD4T cells through increasing the proportion of $CD4^{+}CD25^{+}Foxp3^{+}$ regulatory T cells (Tregs), which play an essential role in maintaining immune tolerance under physiological conditions [55].

The recent literature suggests that oxidative stress plays a central role in the pathogenesis of PD [56]. Neuroinflammation