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Biomedical Applications of Bee Venom: A Natural Approach to Cancer, Infections, and Inflammatory Diseases

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Abstract

Bee venom (BV), a complex honeybee *Apis mellifera* excretion, has been vastly valued throughout centuries for its medicinal virtues, such as described in ancient documents including the Vedas, Quran, and Bible. Modern biomedicine research has elucidated principal bioactive components of BV, including melittin, phospholipase A2 (PLA2), apamin, mast cell-degranulating peptide, and adolapin, which are vested with a wide range of therapeutic properties. Melittin, the principal peptide, is strongly anticancer against a variety of cancers including breast, cervical, prostate, and hepatocellular carcinoma. With nanocarrier systems, it increases delivery and decreases systemic toxicity. Outside of cancer, BV has strong antimicrobial activity against multidrug-resistant bacteria, fungi like *Candida albicans* and *Aspergillus fumigatus*, and enveloped viruses like HIV and flu. BV controls signaling pathways like NF-κB and JAK/STAT3 to suppress oxidative stress and cytokine release. This is beneficial in the treatment of inflammatory and neurodegenerative diseases. BV promotes insulin release and protects against destruction of pancreatic β-cells, and hence can be used to treat arthritis, multiple sclerosis, Alzheimer's, and diabetes. In dermatology and dermal cosmeceuticals, BV inhibits the 5α-reductase activity and promotes hair growth by upregulating growth factors such as FGF7, VEGF, and IGF-1. It is also useful in the treatment of acne, psoriasis, and vitiligo. Apipuncture, which is the interaction of traditional acupuncture with bee venom pharmacology, has also been shown to be useful in randomized controlled trials for musculoskeletal pain, rheumatoid arthritis, and neurological disorders. Although its multistage therapeutic potential is encouraging, clinical use is a limitation due to variability in venom composition, standardization of dosing, immunogenicity, and long-term safety. Optimal extraction methods, molecular identification, and unraveling the synergistic interaction of BV components need to be a focus of future studies to establish effective, safe, and targeted therapies. Further studies are indicated to explore the promise of bee venom as a natural addition to precision medicine across various fields.

Keywords: Bee Venom (BV), Cancer, Infections, Inflammatory Diseases

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INTRODUCTION

Despite advances in modern medicine, natural plant and animal products remain important for disease prevention and treatment. Many Western therapies originated in Asia and are becoming increasingly popular worldwide. Insect venoms, particularly *Apis mellifera* venom, have been used in traditional and alternative medicine for many years. Bee venom is well-known for its therapeutic potential in modern drug development. The medicinal use of bee products is mentioned in ancient texts, including the Holy Vedas, Quran, and Bible. This is due to the fact that much research has been carried out on the bee venom secreted in the venom gland which is found inside the abdominal cavity of the honey bee. One sting from a solitary bee conveys 50 µg to 140 µg of the venom, though the venom sac can hold over 300 µg.[1] Bee stings may lead to reactions that are both local and systemic in the victim. Consequently, insects of the order Hymenoptera normally produce similar local reactions when they sting because their toxins are similarly composed. Systemic reactions depend on the allergens contained in BV.

Chemotherapeutic interventions may include hormone therapy, chemotherapy, surgery, radiation therapy, or any combination of these. All these have numerous side effects. Competitively inhibiting estrogen, drugs are given. Circulating estrogen may be reduced either by binding to the estrogen receptors or by inhibiting the conversion from androgen to estrogens. Such drugs are routine in hormone therapy but are accompanied by side effects including osteoporosis, arthralgia and myalgia, hot flashes, and endometrial carcinoma. Chances of recurrence can be reduced using chemotherapy, inhibiting DNA replication or cell division.[2] The side effects of this treatment are leukemia, myalgia, weakness, and edema. Postmastectomy radiation therapy reduces the chance of local recurrence and enhances survival rates. Many cancer patients seek alternative and complementary therapies to better address side effects of standard treatments. Natural products from plants or animals are used as medications for diseases.[3] The bee venom constituents of Apis have a wide range of biological activities, including anti-inflammatory, anti-arthritic, anti-cancer, anti-microbial, and anti-protozoan properties. *Apis mellifera* honeybee venom contained antibacterial peptides and enzymes. Few peptidergic subfractions were isolated and purified that were considered as responsible elements for inflammation and pain-related behaviors.[4] Among them four active peptidergic elements were determined: melittin, phospholipase A2-related peptide, apamin, and mast-cell degranulating peptide (MCDP).

Major component of bee venom and its multifaceted mechanisms

Bee venom (BV) is a multifaceted biological complex of highly active therapeutic peptides and enzymes. The major constituent, melittin, constitutes nearly half of the dry venom and possesses various pharmacological activities, including anticancer, antimicrobial, and anti-inflammatory effects. It targets membranes, nociceptive neurons, and signaling pathways such as JAK/STAT3, NF-κB, and MMP. Melittin has high anticancer activity, inhibiting tumor development and metastasis in prostate, ovarian, and hepatocellular cancers,[5,6] but its cytotoxicity and hemolysis limit its clinical use. Nanoparticle-based delivery systems, particularly niosomes, have been shown to be new in optimizing treatment efficacy with few side effects.[7]

Apamin, phospholipase A2, and mast cell-degranulating peptide are three more BV peptides of great pharmacological significance. Apamin is a neurotoxic peptide whose action is to selectively inhibit small-conductance Ca^{2}z-activated Kz channels, which influence the function of neurons and potentially cure neurodegenerative diseases like Parkinson's.[8] PLA2, which accounts for 12%-15% of the venom, hydrolyzes cell membrane phospholipids and, with melittin association, generates cell lysis, influencing inflammation and immune modulation.[9] MCDP or peptide 401 causes histamine release from mast cells and, depending on its concentration, has pro-inflammatory and anti-allergic properties.[4] Other substances, adolapin and hyaluronidase, increase BV's bioactivity. Hyaluronidase hydrolyzes hyaluronic acid of connective tissues, enabling venom diffusion and systemic absorption as well as pro-inflammatory reaction and allergic sensitization.[10] Adolapin, a 103 amino acid polypeptide, has

Table 1. Composition of Bee Venom and Pharmacological Effects

Component	Function	Therapeutic Effects	Author
Melittin	Main peptide (40%-60% of dry weight)	Anticancer, anti-inflammatory, antimicrobial	Moghaddam et al.[7]
Apamin	Neurotoxic peptide	Neuroprotective, improves cognitive function	Gu et al.[8]
Phospholipase A2	Enzyme	Pro-inflammatory and immunomodulatory	Pereira et al.[9]
Mast Cell Degranulating Peptide (MCDP)	Histamine-releasing	Modulates allergic and inflammatory responses	Wehbe et al.[4]
Hyaluronidase	Spreading factor	Increases tissue permeability	Rady et al.[10]
Adolapin	Peptide	Anti-inflammatory, analgesic	Cherniack et al.[11]

anti-inflammatory, analgesic, and antipyretic activities by inhibiting cyclooxygenase and prostaglandin synthesis, similar to nonsteroidal anti-inflammatory drugs (NSAIDs).[11] Together, these compounds make bee venom an extremely potent therapeutic agent that is active against cancer, inflammation, and neurodegeneration; but with the appropriate delivery mechanisms in place, toxicity can be avoided while efficacy is ensured (Table 1).

Enhanced efficacy

The works have also stated the enhanced potency of doxorubicin co-delivered with melittin using citric acid-functionalized Fe_3O_4 magnetic nanoparticles (CA-MNPs) in inhibiting MCF-7 breast cancer cells[12] wherein the free drug delivery strategy is surpassed by increased cellular uptake and cytotoxicity.[13] The synergistic strategy conforms to earlier work on the anticancer properties of melittin, such as induction of cell death in ovarian cancer cells. The findings indicate that this co-delivery approach could be applied to other forms of cancer like ovarian cancer, where melittin had a positive effect. Further research on these mechanisms may then result in enhanced internalization efficiency and consequently cytotoxic effects from the nanoparticles, thereby offering a foundation for more effective treatments against cancer.

Role of BV on the cancer cell lines

Bee venom (BV) has been shown to have potent cytotoxic and antiproliferative effects on a variety of cancer cell lines, particularly cervical carcinoma. According to research, the cytotoxic action of BV is time-dependent, with HPV-positive cell lines (HeLa and CaSki) being more vulnerable than HPV-negative ones (C33A). In HeLa and CaSki cells, BV treatment reduced mRNA and protein expression of HPV E6 and E7 oncogenes while reactivating tumor suppressor proteins p53 and Rb. BV also decreased cyclins A and B while increasing p21 and p27, thereby effectively inhibiting cell proliferation.[14] Its anti-cancer effects included significantly inhibiting cell migration and wound healing, as well as inducing apoptosis,[15] as evidenced by a decrease in anti-apoptotic proteins Bcl-2 and Bcl-XL and an increase in pro-apoptotic BAX. These events were linked to the activation of caspases 3 and 9, PARP cleavage, and inhibition of key mitogenic pathways such as AKT, JNK, p38, and ERK phosphorylation.[16,17]

Similarly, BV and its major component, melittin, have a strong anti-tumor effect on prostate cancer cells such as LNCaP, DU145, and PC-3. At concentrations of 1-10 µg/ml (BV) and 0.5-2.5 µg/ml (melittin), these compounds cause apoptotic cell death without increasing proliferation. Downregulation of NF-κB, a transcription factor required for androgen signaling and cancer cell survival is a key mechanism. Although melittin-induced apoptosis does not require NF-κB inactivation directly, this suppression alters apoptotic regulation by promoting pro-apoptotic signaling and suppressing survivin activity.[18] *In vivo* studies in mice implanted with PC-3 cells showed that BV at 3-6 mg/kg significantly reduced tumor growth and enhanced apoptosis via NF-κB/caspase pathways, indicating both *in vitro* and *in vivo*

Table 2. Bee venom's ability to cause apoptosis and prevent cancer cell line proliferation

Cell Lines	Result	Author
MCF-7 cells	suppression of human breast cancer cell proliferation, induction of apoptosis	Gao et al.[12]
NCI-H1299	Induce apoptosis-related morphological changes	Jia et al.[15]
A549 cell line	Induced Apoptosis	El-Bassiony et al.[14]
HeLa cell line	Proliferation and metastasis were suppressed	El-Bassiony et al.[14]
HL-60 leukemia cell line	Suppression of proliferation and induction of apoptosis	Cevik et al.[19]
Human melanoma cell line A2058.	Induced Apoptosis	Manceau et al.[18]
MHCC97L cells	Proliferation and metastasis were suppressed	Cui et al.[2]
Human Prostate. Cancer LNCaP, DU145, and PC-3 cells	Apoptosis induction and proliferation suppression	Graff et al.[24]
Hepatocellular carcinoma cell line [BEL-7402].	Initiated Cell Death	Cui et al.[2]
Human prostate cancer cell line (PC-3)	Inhibition of viability through control of genes linked to the cell cycle and HPV oncogenes	Cevi et al.[19]

efficacy in preventing prostate carcinogenesis[19] (Table 2).

The biological functions of bee venom

Antimicrobial properties

It has been proven that honey bee venom contained antimicrobial properties against many pathogens, including viruses, fungi, and bacteria (Figure 1). Honey bee venom had highly potent antibacterial activity against drug-resistant strains as well as against Gram-positive and Gram-negative bacteria. Honey bee venom also exhibited antifungal activity against various pathogenic fungi, such as *Candida albicans*.[20] The primary component of honey bee venom responsible for its antimicrobial action is melittin, which is a small peptide that ruptures the cell membranes of microorganisms and finally kills them. Melittin represents a good possibility for producing original antimicrobial drugs, as this compound demonstrates the low toxicity of mammalian cells along with high broad-spectrum antimicrobial activity. Melittin and the other peptides with low molecular weight metabolites, play a central role in antimicrobial activity for BV.[21] In addition to melittin, in the venom of honey bees, other active products have also been discovered-apamin and adolapin with its antimicrobial properties. These compounds interact with melittin to enhance the overall antimicrobial activity of honey bees venom. Dosage and safety are thus the two major issues that arise in the use of bee products in medicine. Due to complexity and wide variety of possible composition of these products, standardization is required prior to achieving safe and clinically effective use.[22]

Figure 1. Pharmacological properties of Bee Venom

Antibacterial activity

Bee venom substance has been used since ancient times of traditional medicine

Table 3. Therapeutic Application of Honeybee venom

Therapeutic Effects	Applications	Author
Anti-inflammatory	Bee venom helps reduce inflammation and protects connective tissues. It's possibly helpful for conditions like arthritis, rheumatism, multiple sclerosis, and lupus.	Singh et al.[34]
Central Nervous System Diseases	Contains enzymes and peptides that might help treat diseases like ALS, Parkinson's, and Alzheimer's.	Gu et al.[8]
Antimicrobial Properties	Rich in peptides and enzymes that kill harmful microbes, making it useful for fighting infections.	Isidorov et al.[21]
Cytotoxic Antitumor Effects	Compounds like melittin can kill tumor cells in lab tests, suggesting potential use in cancer treatment.	Moghaddam et al[7]
Immunomodulatory Effects	It can regulate the immune system, which may help treat autoimmune diseases and boost the body's defenses.	El-Seedi et al.[26]
Standardization Challenges	It's hard to set safe doses because bee venom varies in composition, so standardization is needed for clinical use.	Leccia et al.[36]
Combined Treatment Benefits	When used with chemotherapy, bee venom reduces cisplatin build up and helps prevent resistance to the drug.	Shiassi et al.[35]

based on its anti-inflammatory, analgesic, and antimicrobial properties. The activity of bee venom against a number of bacterial species, including *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* done for their anticapsular activity.[23] The scientists stated their vision of the efficiency as a natural alternative to conventional antibiotics, which can be used in the therapeutic treatment of bacterial infections. Peptides of BV has shown bacteriostatic activity against multidrug-resistant bacteria, including CRE and MRSA. This highlights the potential of natural compounds as alternative antibacterial agents in the fight against antibiotic-resistant infections. However, clinical application would require careful evaluation of delivery methods and safety profiles to ensure efficacy and minimize risks.[24]

Antiviral activity

Increasing research interest about BV compounds antiviral properties by recent years on the enveloped viruses such as HIV, HSV and influenza have drawn attention recently. BV disrupts the lipid bilayer of virus envelopes, preventing the virus from penetrating host cells. It also inhibits attachment and entry of the influenza A virus, virus replication *in vitro* is thus prevented.[25] Similarly, melittin has been found to inhibit the fusion of the viral and host cell membranes that prevents the replication of the herpes simplex virus.[23] Bee venom [BV] also contains other bioactive components containing antiviral properties aside from melittin. One of the neurotoxins present in bee venom, called apamin, has been proven to suppress the replication of HIV by preventing the entry and integration of the virus into the host cells. In addition, an enzyme found in bee venom called phospholipase A2 has shown antiviral activity against respiratory syncytial virus by destroying the integrity of the viral envelope. Adenovirus and influenza A have been demonstrated to be affected by melittin and bee venom. By promoting the production of interferon they boost antiviral defenses and damage viral membranes. The venom of honey bees is also being studied as a potential SARS-CoV-2 drug.

Antifungal activity

Bee venom shows anti-fungal activities against the opportunistic pathogen *Candida albicans*, which causes an infection in humans. Bee venom led to the destruction of the cell membrane of fungi and resulted in cell death in *C. albicans* by inhibiting its growth with the dose given in proportion. The antifungal activity of bee venom against *Aspergillus fumigatus*, a fungus that has been identified as a cause of severe respiratory infections in immunocompromised people. The venom of bees inhibited the growth of *A. fumigatus* through the disruption of its cell wall, causing apoptosis in fungal cells. It served as an antifungal compound in terms of action through cell membrane interference and triggering caspase/mitochondrial pathway-

mediated programmed cell death. Bee venom, in several killing-curve and broth microdilution and disk diffusion assays, exhibited promising activities against numerous yeast strains derived from vaginal and blood samples. Compared to fluconazole, bee venom exhibited more significant antifungal activity against *Trichophyton rubrum* and *Trichophyton mentagrophytes*.[26] It also exhibits high antifungal characteristics against *Malassezia furfur* and *Candida albicans.*[17]

Anti-protozoal activity

Research evidence shows that in the guts of modified mosquitoes where *Plasmodium ookinetes* is present, BV group III sPLA2 may inhibit and prevent trypanosomiasis.[27] Melittin is able to cause damage to cell walls in simple and complex organisms, which has endowed it with germ-killing, anti-fungal, and anti-Leishmania properties. This damage also makes walls more porous and may even burst them. In *in vitro* experiments, PLA2 has proven its ability to combat Trypanosoma brucei. Lazioglossins other bee venom peptides, show excellent germ-fighting abilities by interfering with cell walls and binding to DNA.[28] Scientists have placed melittin in vaccines because it fights *Plasmodium, Trypanosoma cruzi, Toxoplasma gondii*, and *Leishmania*. While we know that bee venom fights protozoa, we need to dig deeper to understand what its parts do, how they work, and if we can use them as medicines.

Anti-arthritis activity

BV has an anti-arthritis effect. It prevents the spread and reduces the levels of inflammatory agents such as PGE-2, cytokines, nitric oxide, COX-2, and TNF-α. Melittin decreases the expression of interleukin-1, tumor necrosis factor (TNF)-α IL-6 reactive oxygen species, and nitric oxide. It also decreases phospholipase A2 and COX-2. BV also

Figure 2. Cosmeceutical Applications of Bee Venom

inhibits NF-κB activation, induces apoptosis in rheumatoid synovial cells, and delays arthritis in mice infected with *Mycobacterium butyricum*. It is effective in reducing inflammation and preventing oxidative damage. BV acupuncture may be useful in the treatment of rheumatoid arthritis and osteoarthritis because it reduces tissue injury and immune responses.[29]

Anti-inflammatory activity

Melittin from bee venom (BV) inhibits signaling pathways and pro-inflammatory cytokines such as p38 MAPK and NF-κB, making it effective in treating neurodegenerative diseases and skin conditions.[30] It also promotes cell survival by inhibiting death factors, implying that it may be used to treat diseases such as blocked arteries and amyotrophic lateral sclerosis (ALS). Other bioactive components of BV, such as phospholipase A2, adolapin, and apamin, contribute to its anti-inflammatory properties, making it useful in the treatment of cirrhosis, arthritis, and respiratory distress. BV can help heal bruises and treat inflammatory and neurodegenerative disorders.[23,31]

Anti-diabetic activity

BV seems to have therapeutic potential in managing a number of diseases such as diabetes mellitus, which raises blood sugar and cholesterol. BV and metformin both proved effective in managing diabetic mice. Melittin, a significant component of BV, activates Ca^{2+} channels through the process of cell membrane depolarization, reduces inflammatory response in the islets of the pancreas, and increases β-cells to secrete more insulin. BV reduces inflammation and has antioxidant effects that improve normal pancreas morphology and function.[32] BV treatment to diabetic mice for 35 days leads to the augmentation of insulin release, regulation of glucose, and improvement in fertility. It further lowers cholesterol and triglyceride and glucose concentrations while raising the concentration of insulin and HDL. The reduction of islet inflammation, control of glucose, and increase in insulin levels have been achieved by the two key components of BV, namely melittin and phospholipase A2. The protective effect on β-cells during this process can be contributed by the inhibition of production of free radicals and proinflammatory cytokines. According to experts, BV can be used as an auxiliary treatment for diabetes and obesity; however, doctors rarely use it in practice. Still, it would have to be further studied on how it would work and was safe.[33]

Biomedical applications of Bee venom

Bee venom exhibits diverse therapeutic effects that make it a promising candidate for various medical applications. Its anti-inflammatory properties[34] can alleviate conditions like arthritis, lupus, and multiple sclerosis by protecting connective tissues. In central nervous system diseases such as Parkinson's, Alzheimer's, and ALS, bee venom's bioactive enzymes and peptides may offer Neuroprotective benefits. Its antimicrobial action, due to the presence of potent peptides and enzymes, helps fight infections, while cytotoxic compounds like melittin show significant antitumor activity by inducing cancer cell death in laboratory settings. Furthermore, bee venom has immunomodulatory effects,[26] making it potentially valuable in treating autoimmune disorders by balancing immune responses. It also shows promise in enhancing chemotherapy efficacy by reducing cisplatin[35] accumulation and resistance. However, standardization challenges due to variation in venom composition highlight the need for precise dosing and clinical validation before widespread therapeutic use (Table 3).

Cosmetic uses of Bee venom

Vulnerary

Today, some of the skin diseases that BV is applied to include vitiligo, alopecia, atopic dermatitis, acne vulgaris, and psoriasis. BV is used in cosmetics and topical formulations; it is also used in face masks and as a dressing for wound healing (Figure 2).

An infected wound will eventually develop into scars and re-epithelialize, which marks the end of a complex healing process. Bee venom, owing to its anti-inflammatory, antimicrobial, analgesic, and antioxidant properties, could act as an adjuvant in healing during wound repair. The studies on the wound dressings doped with BV or chitosan films show significant increases in the rate of wound closure. The collagen expression and β-defensin-2 (BD-2) were enhanced along with the restoration

of levels of angiopoietin-1 (Ang-1) and Nrf2. BV therapy suppressed macrophage apoptosis. The nano fibrous materials with the load of BV also exhibit better activity against *Staphylococcus aureus* and more efficient antibacterial properties in comparison with the commercial antibacterial agents.[33]

Atopic dermatitis

AD is an inflammatory disease of the skin, with little treatment option, and significant adverse effects of treatments that exist at present. Antiallergic, anti-infectious and anti-inflammatory are some of the promising properties with which bee venom (BV) and its constituent peptides have recently been associated through prevention of production of cytokines and signaling pathways like STAT and NF-κB. Recent studies on both animal models as well as in clinical trials found BV to induce significant reduction of symptoms of AD with minimal side effects.[34]

Acne end

Acne vulgaris is one of the most common skin conditions that are more common in teenagers and caused mainly by bacterial colonization and inflammation. Due to the inhibition of NF-κB signaling and the decrease in cytokine levels, it has shown antimicrobial and anti-inflammatory effects both in cell studies and acne patients. Leccia et al., found cosmetics containing benzophenone (BV) were safe to apply, caused slight irritation after prolonged use, and gave excellent therapeutic results for the treatment of acne.[36]

Pattern hair loss

FDA-approved drugs are few in minoxidil and finasteride, which are found to have limited treatment efficiency for the common age-related condition known as androgenetic alopecia (AGA), causing hair loss. Results obtained indicate that bee venom (BV) has the capability to improve hair growth without any noticed side effects since it reduces expression of 5α-reductase and promotes growth factors. BV may provide a better and safer treatment for AGA.[37]

Genetic predisposition remains the primary reason for hair loss, although there is also evidence that stress and infection of the scalp may contribute. Hair loss is a very devastating condition and may affect one's quality of life and self-esteem. According to recent studies, inflammatory disorders are responsible for 74.1% of patients with alopecia, while mental illnesses are responsible for 25.5% of cases. Bee venom (BV) inhibits 5α-reductase and increases keratinocyte growth factor (KGF), which is crucial for follicular proliferation, thus promoting hair growth in mice. While BV treatment does not have side effects such as edema and irritation that have been associated with the use of finasteride and dutasteride, *in vitro* studies indicated that BV stimulates hair growth through cell proliferation of human dermal papilla by upregulating the expression of FGF7, FGF2, VEGF, and IGF-1 during the anagen phase. These results point to BV as a possible treatment option for hair loss.

Wrinkles

Sunlight reduces elasticity to the skin, making it such that the latter becomes ridged and leads to basic wrinkle-causing lines on the face. The need for easy anti-wrinkle treatments led to the innovation of cosmeceuticals, a mixture of medicinal and cosmetic properties. A 12-week clinical study with 22 Korean women aged 30-49 applying a facial serum containing 0.006% BV twice daily with minimal or no irritation possessed the potential in reducing the area, count, and size of wrinkles. Knowledge about the anti-wrinkle effects of BV is scarce. However, cosmetics containing BV as well as BV and bvPLA2-free BV can protect the skin against UVB ray damage and postpone the appearance of wrinkles.

Focal vitiligo

Skin and hair will turn depigmented due to the disorder of pigment called vitiligo, caused by the loss of melanocytes. Repigmentation is a rough and slow process that requires melanocyte migration and proliferation. Although the UVR is the most commonly used therapy, there is still a need for novel approaches. Melanocytes were noted to double in response to bee venom (BV) at concentrations of at least 10 µg/mL. This means that BV is proliferative for melanocytes. In addition to this, BV also stimulates melanogenesis by the activation of tyrosinase and significant signaling pathways, including PKA, ERK, and PI3K/Akt. Ingredients histamine and bvPLA2, which activate

melanocyte migration, will help deliver the ingredients to the vitiliginous NPDS keratinocytes exactly for curing vitiligo.[38]

Psoriasis vulgaris

Psoriasis is a chronic inflammatory skin disease that mainly affects the scalp and extensor regions. The common symptom of this disease is red, scaly plaques. In one study, 25 patients with resistant localized plaque psoriasis (RLPP) were treated with weekly injections of bee venom (BV) for three months. Then, the BV dose was gradually increased to 1 ml. A 92% complete response rate was achieved with only mild side effects, such as erythema, pain, and swelling at the injection site. Further research is necessary for the proper safety and safety of the utilization of BV products because the composition of BV differs from one strain of a bee to another and differs concerning season and environmental influences.[39]

Localized Scleroderma

Localized scleroderma, also known as morphea, is an inflammatory condition characterized by excessive collagen build-up in the skin and subcutaneous tissues, leading to fibrosis. It typically presents as thick, white patches with a reddish-purple hue and may cause itching but is generally not painful. The exact cause remains unclear, but it involves processes such as fibrosis, inflammation, vascular damage, and immune system activation. Currently, there are no established medical therapies for morphea. However, bee venom acupuncture (BVA) has shown promising results, with treatment administered initially in the first week and then every three weeks, leading to significant improvement in skin condition along with reductions in pain and sleep disturbances.

BV apipuncture - A therapeutic function

Apipuncture, also known as bee venom acupuncture (BVA), is a form of therapy derived from traditional Korean medicine that involves injecting purified bee venom into specific acupuncture points on the body. This treatment combines the principles of acupuncture with the pharmacological properties of bee venom, which contains bioactive compounds such as melittin, apamin, and phospholipase A2 known for their anti-inflammatory, analgesic, and antimicrobial effects.[40-43] Clinically, BVA has been increasingly used to manage musculoskeletal pain conditions such as osteoarthritis, rheumatoid arthritis, and low back pain. A recent meta-analysis confirmed its potential effectiveness in reducing pain intensity and improving function in patients with chronic musculoskeletal disorders.[44] Beyond pain management, research has expanded into the broader biomedical effects of bee venom. For example, studies have demonstrated its anti-cancer activity against triple-negative breast cancer cells by promoting apoptosis and reducing cell viability.[45] Additionally, bee venom from *Apis mellifera* anatoliaca was shown to exert anti-inflammatory effects by down regulating pro-inflammatory cytokine production in LPS-stimulated macrophages, highlighting its potential in treating immune-related diseases.[46] Given its multi-target therapeutic actions, BVA is not only a complementary pain therapy but also a promising candidate for further clinical application in inflammatory and infectious diseases.

Veterinary applications of Bee venom

The combination of bee venom and silver nanoparticles (AgNPs) shows promise as an alternative antibacterial strategy against American foulbrood (AFB), a lethal disease caused by Paenibacillus larvae in honeybee colonies. According to recent research, AgNPs possess strong antibacterial properties that are significantly enhanced when activated by visible light. Furthermore, the combination of bee venom and AgNPs has been shown to significantly increase antimicrobial activity and colony health by extending bee lifespan-potentially doubling it when administered as sugar syrup. These findings highlight the possibility of combining natural bioactive compounds with nanotechnology to address bacterial resistance issues caused by conventional antibiotics. Bee venom's anti-inflammatory and immunomodulatory properties have been investigated as potential treatments for chronic bee paralysis virus and Nosema infections. These treatments, when optimized for dosage and delivery, have the potential to transform apiculture practices by offering long-term, biologically compatible bee health management options.[40]

Its anti-inflammatory and analgesic properties have been used to effectively treat canine intervertebral disc disease, with BV injections at acupuncture points improving neurological function and shortening recovery time. Broiler growth performance, immune response, and meat quality have all been shown to improve with BV supplementation. BV's antifungal properties have been demonstrated to be effective against dermatophytes such as Microsporum canis, implying that it can treat fungal infections in animals. Because of its numerous advantages, bee venom is an important tool for improving veterinary therapeutics and welfare.

Randomized Controlled Trials RCTs

Randomized Controlled Trials (RCTs) are the standard against which all other study designs are measured in determining the efficacy of treatments and their safety. RCTs have been used to test whether bee venom can be used to treat illnesses. Bee venom is a mixture of many active ingredients. It has been used by humans for centuries to treat pain, inflammation, and arthritis. But have researchers begun experimenting with it using RCTs. A 2018 RCT reveals that bee venom acupuncture (BVA) benefited individuals with chronic low back pain. It reduced their pain and improved their lives relative to those that did not get the treatment.[47] A 2019 RCT study states that BVA benefited patients with rheumatoid arthritis. It increased their symptoms and made them walk longer. Side effects were minimal. Academic Press in 2020 has accounted for bee venom therapy having improved multiple sclerosis patients. They thought more clearly, and fatigue significantly improved.[48]

An RCT in 2017 has established that BVA had reduced the pain of cancer patients. From the EU Clinical Trials Register, we have no human trial yet that confirms bee venom to be effective.[49] But from CTIS, we do know that there are 43,977 clinical trials with an EudraCT protocol. Of these, 7,312 are still ongoing. We have no way of knowing how many of them test bee venom therapy. Large-scale trial of bee venom was performed in 2016. It assessed whether bee venom enhanced functioning in individuals with Parkinson's disease. This RCT revealed that bee venom didn't help to help the participants move better compared to a placebo therapy. There is also more research that is being carried out, and so we haven't yet heard whether it works or not and whether it's safe to have as treatment. Bee venom is capable of inducing superficial or more severe problems, such as increased hypersensitivity reactions. Science cannot demonstrate that it works and is safe to take. Conversely, external lotion along with bee venom and ultrasonography gel is applied most frequently for the condition of temporomandibular disorders as well as for myalgia.[50]

Future use

Currently, raw and its extracts of BV are used widely in various countries for treating numerous health disorders including hepatic disorders, arthritis, neurodegenerative diseases, infections, skin infections, as well as cancers. BV also exhibits anticancer and antimicrobial properties. Earlier research enhanced our knowledge on the composition and biomedical applications of BV. On the other hand, BV still has limited applications in clinics. In addition, better standardization of extraction methods is required for long term viability. Therefore, there is an important need for more research on BV and its components so that their physicochemical actions and therapeutic effects can be well understood. Consequently, attention will increase for BV in advanced medicine. In addition, the knowledge of the molecular structure of BV could be a breakthrough in developing novel therapies based on the biochemical characteristics of this substance. Better methods of extraction and purification may provide formulations that are reproducible and potent for use in the clinic. In addition, studies into possible synergies among the components of BV might form a basis for the choice of targeted and disease-specific therapy in different medical fields.

CONCLUSION

Bee venom (BV) is a high-potency bioactive natural product with diverse therapeutic and cosmetic applications against cancer, infectious, autoimmune, neurodegenerative, and inflammatory diseases. Melittin, phospholipase A2, apamin, and other ingredients have a wide variety of biological activities varying from targeting

microbial membranes, immunomodulation, and inflammatory response modulation to inducing apoptosis in cancer cells. The integration of BV and advanced delivery systems, such as nanoparticles, has the promise of highly increasing the specificity of treatments with reduced toxicity, particularly in precision medicine and cancer. Clinical translation is hindered in the face of encouraging preclinical and clinical data in support of the efficacy of BV in such diseases as arthritis, diabetes, acne, and alopecia, by variability in venom composition, dose standardization, allergenicity, and safety concerns such as anaphylaxis. These limitations highlight the demand for rigorous standardization of extraction process, formulation development in controlled environments, and well-designed randomized controlled trials to validate therapeutic claims and protect patients.

Future requirements for long-term safety profiling, optimized delivery mechanisms, and increased research into the molecular mechanisms of action of BV's bioactive constituents will be necessary for it to realize its full potential as a reliable adjunct or alternative in modern therapeutics and cosmeceuticals. With further scientific advancement and clinical validation, bee venom could develop from a folk medicine to a standardized, effective, and safe drug, bringing new answers for multifactorial disease treatment as well as dermatological disease treatment in modern medicine.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

YS performed assessment. YS, SSI and JPR wrote the initial draft. PB, YS, JPR, SK, SSI and SSA reviewed the manuscript. SSI wrote the manuscript. PB, YS, JPR, SK, SSI and SSA edited and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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