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Author's Affiliation:
1. Department of Science Laboratories, College of Science and Arts, Qassim University, Ar Rass - Saudi Arabia
2. Department of Zoology and Entomology, Faculty of Science, Assiut University, Assiut - Egypt

Corresponding Author:
Ahmed. M. H. Ali
Email: shafa2000us@yahoo.com

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Advancements in bee venom bioactivities for current therapeutic applications: A Review

Ahmed. M. H. Ali[1,2]

Abstract

Bees, as a distinguished lineage of hymenopteran insects, have undergone significant evolutionary adaptations, transitioning to a pollen-based provisioning strategy for their offspring and diverging from a reliance on prey. Within the intricate composition of bee products lies a myriad of chemicals that have garnered widespread recognition for their therapeutic and health-enhancing attributes. Bee venom, a constituent of apitherapy deeply embedded in traditional medicine with a millennia-long historical foundation, is a subject of considerable interest. Honeybees, among various bee species, manifest considerable, albeit variable, levels of antioxidant, antibacterial, and anticancer activities in their venom. This variability underscores the need for a comprehensive exploration of the diverse applications of bee venom. The present review, thus, seeks to systematically collate and analyze pertinent scientific literature, shedding light on the multifaceted roles of bee venom across various therapeutic domains. Moreover, the review evaluates the extant evidence supporting the therapeutic use of bee venom, identifying gaps and limitations within the existing body of research. By synthesizing recent advancements and critically examining the scientific landscape, this review contributes to the evolving understanding of bee venom bioactivities and offers a foundation for advancing their applications in contemporary therapeutic settings.

Introduction

In the last decades, the world has witnessed a growing interest in natural products and utilization of these products in food, medicine, cosmetics and many more [1]. Among these products are honey as well as other honey products. The history of human use of honey and bee products is not precisely defined, however, it is thought that it dates back to 10,000 years [2]. The ancient Egyptians, Greeks, Romans, and Chinese all used bees and their products for medicinal purposes. Honey was employed by physicians in ancient Egypt as a component of therapeutic compounds, dating back 5,000 years. Additionally, the ancient Greeks held the belief that honey had the ability to enhance both virility and lifespan. Honey has been used in traditional Chinese medicine for hundreds of years and continues to be important now. Honey was recognized as a highly valued medicinal treatment in ancient Russian writings [3]. A Muslim physician described the medical virtues of honey in the late 12th century, including its ability to transport physiological fluids, reduce stomach pain, treat dropsy, control facial spasms, promote hunger, prevent muscular degradation, and retain muscle mass. According to the Quran, bee products played an important role in medicine from the eighth to the fourteenth centuries [4].

Bee venom has been used widely in traditional medicine throughout history to treat a broad variety of health issues. According to reference [5], bee venom was used for medicinal purposes in ancient Egypt, Greece, and China. In recent years, bee venom treatment has been used to treat conditions such as arthritis, multiple sclerosis, and chronic pain.

Hippocrates, the Greek physician, used bee venom to relieve pain, reduce inflammation, and treat ailments like gout and other maladies. Traditional Chinese medicine has always employed bee venom to treat ailments such as rheumatoid arthritis and skin problems. Ancient Egypt was one of the earliest civilizations to mention the use of bee venom to treat joint pain and inflammation.

Bee venom treatment, according to the American Apitherapy Society, is a viable therapeutic alternative for illnesses such as arthritis, multiple sclerosis, and chronic pain [6]. Nonetheless, it is critical to recognize that the use of bee venom treatment is controversial and lacks universal approval in the medical world.

There is a notable lack of knowledge in scientific literature on the historical uses of bee venom. In addition, the author noted the increasing fascination with bee venom therapy in Egypt as well as in several Middle Eastern nations. Hence, the primary aims of this study were to address the dearth of suitable scientific evidence and to investigate the widespread use of bee venom applications.

Methods

Literature Search Strategy and Selection Criteria

An extensive literature review was performed on honey bees, specifically examining the utilization of bee venom and its associated bioactive compounds. This study utilized many academic databases, including Google Scholar, Scopus, Web of Science, Science Direct, and J-Gate, in addition to a search of peer-reviewed journal papers in the library. This assessment does not include any resources that have not been released. The writers structured, assessed, reviewed, and drew appropriate conclusions from the final data collected through their talks. This research focuses on several major keywords, including bee venom, bees, the taxonomy of bees, biological activity, and chemical structure.

Discussion

Strengths and limitations of the study

This review aims to compile pertinent information regarding the diverse applications of bee venom. Bee venom treatment, an integral aspect of apitherapy deeply ingrained in traditional medicine with a history spanning millennia, is a central focus of investigation. However, it is essential to consider the findings within the context of certain constraints, such as: (i) Data Limitation: The review encountered restrictions due to a scarcity of accessible data on the uses of bee venom for different diseases. The study focused on publicly accessible data from 2013 to 2023 and discovered a shortage of full information. (ii) Lack of complete understanding of mechanisms: The study found a lack of complete understanding of the biochemical and physiologic mechanisms that underlie the good health benefits associated with bee venom, as stated in published literature. (iii) lack of standardization: While the study revealed that honeybees had antioxidant, antibacterial, and anticancer activity, a notable result was a lack of uniformity in these attributes across various academic opinions and publications. The lack of consistency makes it difficult to correctly evaluate and compare the therapeutic benefits of bee venom in varied applications. (iv) limited clinical data: A key disadvantage is the absence of considerable clinical evidence in the scientific literature supporting the therapeutic use of bee venom. This highlights the need for additional research and confirmation of claims via thorough clinical investigations.

The taxonomy of honeybees

A detailed examination of the categorization of honeybees has been conducted, applying a comprehensive technique that combines morphological, behavioral, and genomic data to uncover distinctions

among multiple species and subspecies. Historically, honey bee classification was mostly based on physical criteria such as body size, colors, and wing structure. The use of molecular tools, on the other hand, has enabled researchers to enhance honey bee categorization and uncover small genetic changes among diverse populations [7, 8]. Bees are members of the Hymenoptera order, which also includes ants, wasps, and sawflies. The order Hymenoptera is characterized by several key features, including the presence of two pairs of wings, a narrow waist between the thorax and abdomen, and a modified ovipositor used for stinging or egg-laying [9].

Currently, the bees are categorized into seven distinct families, namely Colletidae, Stenotritidae, Andrenidae, Halictidae, Melittidae, Megachilidae, and Apidae, with the western honey bee (*Apis mellifera*) being the most well-known, extensively studied, and considered the main species utilized for crop pollination on a global scale [10, 11].

The bee species can be categorized into two main groups based on tongue length, with approximately equal representation (Figure 1). The first group includes the families Colletidae, Stenotritidae, Andrenidae, Halictidae, and Melittidae, collectively referred to as short-tongued bees. The second category comprises the families Megachilidae and Apidae, which are commonly referred to as long-tongued bees [12, 13].

The correct classification of bees bears substantial relevance in appreciating their ecological activities and linkages while also facilitating initiatives connected to conservation and management. Furthermore, it is critical to realize the significant role that bees play in pollination. These insects taxonomic diversity and ecological interactions are critical for sustaining the resilience and survival of many ecosystems [14].

Bee taxonomy is a complicated and ever-expanding subject of study, marked by continuing research that seeks to enhance and update our knowledge of these vital arthropods.

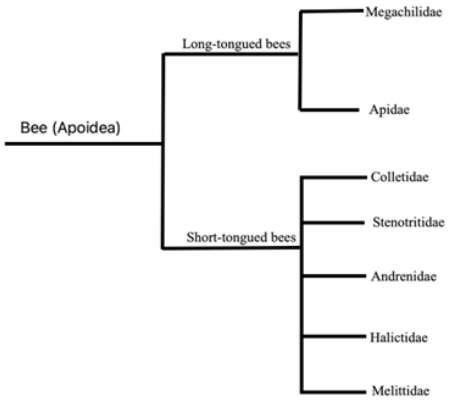

Figure 1: Phylogenetic interconnections among bee families.

The source of venom

Bee venom is generated in the venom gland of female honeybees, which is situated in the abdominal cavity [15]. For containment, the gland is anatomically attached to a surrounding sac. The viniferous apparatus, found in Apis social insects, is an important defensive system. Bees engage in stinging behavior around the apiary as a means of protecting their colony. In contrast, the queen bee employs a stinging mechanism as a means to eliminate competitors. In a hive, the presence of many queens can lead to one of three outcomes: either some queens and a group of bees leave the hive, a born queen eliminates the unborn queens within their cells, or two queens fight in lethal combat [16, 17]. The composition of venom undergoes alterations over time as an individual ages [18].

Bee venom and its medical uses in traditional medicine

The historical use of several bee products, such as bee venom and honey, may be traced back to ancient times. References to their medicinal properties are documented in religious literature that spans several thousand years. Apitherapy is a branch of alternative medicine that involves using several chemicals obtained from honeybees, such as honey, pollen, propolis, royal jelly, and notably bee venom, also known as apitoxin [19, 20].

Honey is well acknowledged as a potent natural treatment for promoting wound healing. Ancient civilizations such as the Chinese, Egyptians, Greeks, Assyrians, and Romans used different types of honey to cure wounds and intestinal disorders.

Antimicrobial Activity

The scientific literature extensively describes the antibacterial effect of honey, namely its biological activity. Honey has been found to possess notable antibacterial effects against the bacterium *Staphylococcus aureus*. An independent study has shown that honey possesses significant antimicrobial properties against different strains of bacteria, including *Bacillus cereus* (a type of Gram-positive bacteria) and *Pseudomonas aeruginosa* (a type of Gram-negative bacteria), as well as yeasts like *Candida albicans* and *Saccharomyces cerevisiae* [21, 22]. A new study has confirmed the antibacterial efficacy of honey against Gram-positive bacteria, specifically *Staphylococcus aureus* and *Enterococcus faecalis*. [23]. Honey derived from honey bees demonstrates a wide range of antibacterial capabilities, effectively against many bacterial, fungal, and viral diseases [24, 25].

Anti-Inflammatory Activity

Animal studies have shown that honey bees possess anti-inflammatory effects. The topical use of *M. marginata* honey has been shown to possess anti-

inflammatory qualities, as evidenced in a specific study [26]. The assessment of the production of inflammatory cytokines has been carried out by exposing human monocytes to Manuka honey [27].

Antioxidant Activity

Multiple studies have shown that honey bees from different geographical areas possess sufficient but differing levels of antioxidant activity. Studies have discovered that honeys obtained from stingless bees demonstrate significant antioxidant properties [28]. A research study conducted in Brazil revealed that honey obtained from *Melipona seminigra*, a kind of stingless bee, demonstrates significant antioxidant properties [29]. Based on the results, Tualang honeybees have significantly higher radical scavenging activity, and their honey shows the most significant antioxidant activity compared to other types of honey [30]. The antioxidant activity of honey has been reported to be attributed to the presence of flavonoids and polyphenols [31]. Previous studies have indicated that Algerian and Bangladeshi honeys exhibit notable antioxidant properties [32, 33].

Neuroprotective Effects

Studies have investigated the possible therapeutic effects of bee venom as an anti-neuroinflammatory agent. Additionally, it has been studied as a chemical that may improve the efficiency of some medications in the treatment of neurodegenerative illnesses while also minimizing their negative effects [34].

Research was conducted in 2015 to investigate the use of BV in the treatment of neurological diseases [35]. Bee venom was used as a therapeutic intervention for dogs with intervertebral disc illnesses, according to the researchers. Intervertebral disc disease is a painful medical condition that necessitates the use of analgesics and anti-inflammatory drugs to alleviate pain and nociceptive signals. Furthermore, there is sufficient evidence to support the efficacy of BV in treating peripheral neuropathy caused by vincristine treatment. Chemotherapeutic medicines may injure sensory and motor neurons in the peripheral nervous system, resulting in peripheral neuropathy [36]. The data suggest that BV might be a potential therapy option for vincristine-induced peripheral neuropathy.

Antitumor Effects

In recent years, there has been a significant increase in the effort to uncover natural compounds that may slow the progression of cancer. Multiple studies investigating the effectiveness of honey in the treatment of different forms of cancer have consistently demonstrated its ability to facilitate the elimination of deceased tissue and promote the development of fresh blood vessels [37, 38]. Multiple studies have extensively recorded the beneficial impacts of honey in battling many types of cancer, including those that affect the oral, bladder, cervical, liver, bone, and breast areas [39- 41]. A research study was conducted to assess the effectiveness of honey in inhibiting the growth, survival, and spread of cancer cells, particularly in terms of their stability, viability, and metastatic potential. The study's findings revealed substantial anti-angiogenic properties associated with honey [40]. As far as current information is concerned, there are existing reports on the anticancer properties of bee propolis [37, 42]. Insufficient data exists on the anticancer properties of stingless bee honey, necessitating further research to comprehensively explore this topic.

Clinical Applications

The anti-inflammatory properties of bee venom have been seen in several inflammatory digestive illnesses, including gastric ulcers, nonalcoholic steatohepatitis, ulcerative colitis, and acute liver failure. The renal organ has also been demonstrated to benefit from the physiological impacts of apitoxin. Scientific evidence has shown that BV and its main constituents are effective in reducing acute kidney damage and renal fibrosis [43- 45]. Parkinson's disease and Alzheimer's disease, both categorized as neurodegenerative conditions, arise from anomalies in the nervous system that cause disturbances in neurotransmitters and the accumulation of misfolded proteins. *Bacillus velezensis* (BV) and its primary constituent have demonstrated neuroprotective properties, potentially impeding the advancement of degenerative diseases. The stated findings mostly consisted of improved motor function, diminished memory deficits, suppressed oxidative stress, reduced neuroinflammation, safeguarded neurons, and averted apoptosis. Moreover, BV and its primary constituents have demonstrated the ability to protect the brain against many neurological illnesses [46- 48].

Chemical constituents of bee venom

Bee venom is a complex mixture of bioactive peptides and enzymes that have various physiological effects. It has been extensively utilized for medicinal reasons and is gaining popularity as a potential therapeutic agent for a variety of ailments. Melittin, adolapin, apamin, and phospholipase A2 (PLA2) are the primary components of bee venom. These chemicals are responsible for bee venom's many biological and pharmacological characteristics. The goal of this research is to give a detailed assessment of the chemical elements found in bee venom, as well as their specific biological properties and prospective medicinal uses [49, 50].

Bee venom contains a diverse set of peptides and enzymes, with around 20 distinct components

discovered so far [51] (Figure 2). Melittin, adolapin, apamin, and phospholipase A2 (PLA2) are the primary bioactive components responsible for the different biological and pharmacological activities of bee venom [52]. Melittin, a peptide consisting of 26 amino acids, is the major component of bee venom. It has been shown to possess a wide spectrum of biological activities, including antiviral, antibacterial, and anticancer properties [53]. Apamin is a neurotoxin that selectively inhibits calcium-activated potassium channels with low conductance. It is now being studied for its possible application in the treatment of epilepsy and Parkinson's disease [54]. Adolapin, a peptide discovered in bee venom, has anti-inflammatory characteristics and has the potential to cure rheumatoid arthritis [55]. PLA2 is an enzyme that facilitates the breakdown of phospholipids in cell membranes and has been linked to several inflammatory disorders [56].

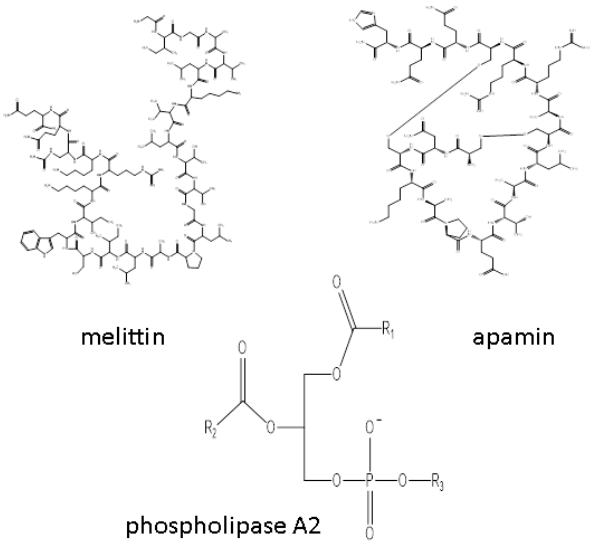

Figure 2: Chemical structure of the main components of bee venom.

Apitherapy has been used for human remedies for thousands of years, and many religious writings, including the Veda, the Bible, and the Quran, mention its medicinal value. All bee products, including raw honey, beeswax, royal jelly, propolis, pollen, and bee venom, are used in apitherapy [57] (Figure 3). Therefore, apitherapy belongs to traditional medicine, which is an important part of medicine despite the neglect of modern medicine, but there is increasing evidence of its effectiveness with minimal adverse effects, and those who use traditional medicinal prescriptions tend to be more health-conscious and more inclined to participate in good behaviors [58, 59].

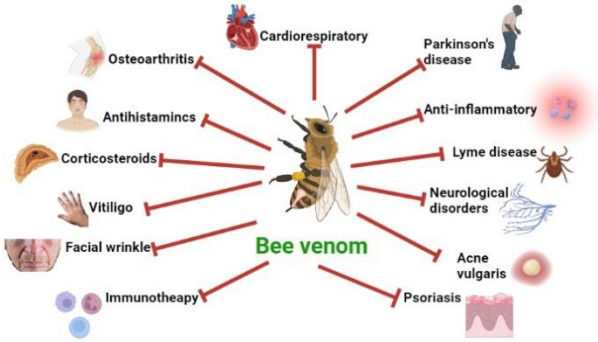

Figure 3: Traditional applications of bee venom

Future prospects

Understanding the chemical constituents of bee venom and their biological activities is crucial for the development of new therapeutic agents and the improvement of existing treatments.

The clinical implementation of BV therapy is now in its early stages, but experts are optimistic that continued research in this area will eventually establish bee venom and its chemicals as viable options for many therapeutic applications in the future. Moreover, in the future, it is important to further explore the many biological and physiological effects that bee venom has on both animals and humans, both in vitro and in vivo. Likewise, the historical use of bee venom in traditional medicine for various illnesses suggests potential for medicinal treatments.

Conclusion

Honey exhibits a wide range of biological, biochemical, and physiological activity in both animal and human organisms. Bee venom has a rich history of use in traditional medicine for treating a variety of ailments. The effectiveness of these qualities is contingent upon the specific phenolic chemicals found in the honeybee. Various varieties of honey have been examined in scientific studies to explore their potential antibacterial, anticancer, and antioxidant characteristics. Regrettably, there has been a lack of systematic research undertaken on bee honey, resulting in limited availability of knowledge on the subject matter. A limited number of studies have documented the advantageous effects of honey in various circumstances. The material presented in this analysis highlights the necessity of assessing the diverse range of biological and pharmacological properties associated with honeybee products.

Author Contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Conflict of Interest

The authors declare that there is no conflict of interest.

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