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REVIEW ARTICLE

MEDICINAL PROPERTIES OF PLANT–DERIVED COMPOUNDS FOUND IN BEE VENOM

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Abstract: Bees are the most important pollinating insects of plants. They perform this function involuntarily by carrying on the pollen that falls on them when they feed on floral nectar. The nectar nutrient content and composition vary among plant species. Nectar is an aqueous solution of sugars, amino acids, minerals, and plant-derived compounds such as alkaloids, phenolics and terpenes. Apitherapy is an alternative medicine used instead of conventional medicine to treat health problems. Current studies have focused on the beneficial effects of bee's venom injection, a branch of apitherapy, at local sites. Many of the components of bee venom exhibits several biological properties such as hepato-protective activities, anti- cardiac arrhythmias, antituberculosis, antioxidant, anti-inflammatory, antibacterial and antiviral activities. Currently, there have been described at least 18 molecules in the bee venom as active components exhibiting pharmaceutical properties. Bee venom is a colorless, bitter and acid liquid which includes a mixture of several compounds and proteins. The venom gland of bees is responsible for producing the venom which is also known as apitoxin and plays a defensive role. This liquid is mostly water and a low proportion is dry venom, which contains melittin, adolapin, apamin, mast cell degranulating peptide, enzymes, amino acids, sugars and some volatile compounds. The volatile components of apitoxin include terpenes, phenolics and alkaloids.

Keywords: Medicinal properties, Bee venom, Plant-derived compounds, Phenolics, Terpenes

INTRODUCTION

Bees are the most important pollinating insects of plants. They perform this function involuntarily by carrying on the pollen that falls on them when they feed on floral nectar (Requier *et al*., 2023).Nectar is an aqueous solution of sugars, amino acids, minerals, and plant-derived compounds such as phenols and terpenes (Venjakob *et al*., 2022). The honey bee of *Apis mellifera* and *Melipona* species, distributed worldwide, generate from the nectar that they feed themselves several products such as venom, propolis, honey, pollen, and royal jell (Jacinto-Castillo *et al*., 2022). Every bee product has been attributed to a medicinal effect. Apitherapy is an alternative medicine used instead of conventional medicine to treat health problems. Other alternative medicine includes ayurvedic medicine which has described medicinal uses of *Andrographis paniculata*, Papilionaceae plants and *Citrus limon* (Tomar, 2020; 2021a; 2021b; 2022a). The mechanism of action of apitherapy bases in the believing that exposure to bee products such as honey or stings acts as an immune modulator or healing factor, respectively (Wehbe *et al*., 2019). The medicinal properties attributed to apitherapy dates from the empirical observation seen in beekeepers who rarely used to present joint problems. Apitherapy consist in using bee products for instance, the local administration of bee venom (BV) into a patient to treat autoimmune disorders. The therapeutic administration of bee venom, into a

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human body, can be directly or indirectly realized. The indirectly administration requires the extraction of the venom from the bee-stinger and the following introduction of this extract by means of a syringe. On the other hand, the direct way involves a natural sting which inoculates the poison (Zhang *et al.*, 2018). Apitherapy has been effective against inflammatory diseases such as rheumatoid arthritis and other diseases related to the central nervous system (Jagua-Gualdrón, *et al.*, 2020., Son *et al.*, 2007).Other studies have demonstrated apitherapy effectiveness against Alzheimer's disease, cancer therapy and microbial diseases, wound healing, treatment of back pain, skin diseases, atopic dermatitis,among others (Wehbe *et al.*, 2019). Lately, most studies have focused on the beneficial effects of bee's venom injection at local sites(Lin & Hsieh, 2020).Many of the components of bee venom exhibits several biological properties such as immune modulators. Currently, there have been described at least 18 molecules as active components exhibiting pharmaceutical properties. These components may modify the production of cortisol and other cytokines which contributes to the activation of anti-inflammatory properties (Kurek-Górecka, *et al.*, 2020).

The composition of bee venom consists of 88% water and 0.1µg of dry venom. The bee venom is a mixture of peptides that include melittin, adolapin, MCD peptide and apamin, it also contains enzymes, minerals, low molecular weight molecules such as phenolics and terpenes (Awad *et al.*, 2017).

Apipuncture: Bee Venom Injection

Apitherapy includes all those medical applications of bee products to treat health problems. A branch of apitherapy uses honey as a healing factor. Another branch of apitherapy uses pollen and royal jelly as nutraceuticals., and, bee venom therapy is the branch of apitherapy that uses bee venom against several illnesses (Fratellone *et al.*, 2016). Bee venom is naturally administered through bee stings to the patient.Another way of bee venom administration are artificially by means of venom extraction and application to the patient through syringe-injections. Besides, bee venom can be administered topically to the skin through ointments, oils, pastes, cream, lotions, gels, tinctures, and so on (Hwang *et al.*, 2015).

Bee venom therapy, either topical or intradermal administered, is used totreat skin illnesses such as acne, wrinkles, and wound healing (El-Wahed, *et al.*,2021.,Kim *et al.*, 2019., Kurek-Górecka *et al.*, 2020). Besides, this therapy has been used to treat arthritis, pain, and other immune disorders. Bee venom can stimulate collagen production., consequently, improving the appearance of aging in the skin. Some investigations report that bee venom decreases the levels of reactive oxygen species, which is associated to an improvement of the healing process. The proposed mechanism of action asseverates that reactive oxygen species leads to tissue damage and culminates in impaired neovascularization (Lin & Hsieh, 2020).Other authors attribute anti-inflammatory properties to bee venom. Those studies assert that bee venom down regulates the expression of COX-2 and PLA2 which decreases the production of enzymes responsible for the formation of substances that mediate inflammation and pain (Kurek-Górecka *et al.*, 2020).

The cosmetic applications of bee venom bases on the results of some *in vitro* studies. The keratinocytes HaCaT and monocytes THP-1 cell lines secrete pro-inflammatory cytokines after stimulation with *Cutibacterium acnes*. Following those cell cultures treated with BV, the cytokines profile change towards TNF-α induction and an inhibition of the bacteria growing is observed (Kim *et al.*, 2015).Another study involving ICR mice, showed inhibitory effects of BV on *cutibacterium acnes*-induced inflammatory skin disease. In this study mice were infected intradermally with *c. acnes* and one group received placebo and the other a BV treatment. Treatment with BV markedly reduced inflammatory reactions and histological changes compared with the control group. Moreover, the expression levels of TNF-α, and IL-1β were significantly reduced (An *et al.*, 2014). An evaluation of anti-acne properties of purified BV serum in humans showed that six weeks of treatment was effective against mild-to-moderate *acne vulgaris*, with no incidence of serious side effects or irritation (Han *et al.*, 2016).

Bee venom exerts anti-arthritic and anti-inflammatory properties (El-Tedawy *et al.*, 2020., Goo *et al.*, 2021). Some studies induced arthritis in rat models with monosodium urate and complete Freund's adjuvant. In those studies, BV treatment reduced levels of TNF-α, IL-1β and NF-κB., besides, BV exhibited inhibitory activity of the COX pathway (El-Tedawy*et al.*, 2020). BV markedly ameliorated ankle edema and mechanical allodynia in gouty rats (Goo *et al.*, 2021).BV restores levels of growth factors, cytokines and reduces the level of free radicals and accelerates healing.The application of apitherapy against immune disorders includes neurodegenerative diseases. Parkinson's is a neurodegenerative disease characterized by the progressive loss of dopaminergic neurons in the substantia nigra and the presence of Lewis bodies. In this pathology, the behavior of bee venom has been evaluated and its ability to prevent the exhaustion of dopaminergic neurons was found. In this specific case, the treatment contained the survival of dopaminergic neurons (Awad *et al.*, 2017).In the case of Alzheimer's, it is a neuroinflammatory disease of unknown etiology. Alzheimer's treatment by means of bee venom could prevent progression by increasing glucose metabolism in the brain. This will decrease amyloid beta deposits in the hippocampus, thus reducing neuroinflammatory responses, thereby

conferring protection to brain tissue (Hwang *et al.*, 2015).

Main Compounds of Bee Venom

Bee venom is a colorless, bitter and acid liquid which includes a mixture of several compounds and proteins. The venom gland of bees is responsible for producing the venom whichis also known as apitoxin and plays a defensive role. Each bee produces an amount of apitoxin ranging between 50 and 300 µLdepending on the environmental conditions and the species of the bee(Tanuğur-Samanc & Kekeçoğlu, 2021). This liquid is mostly water and a low proportion is dry venom, which contains melittin, adolapin, apamin, mast cell degranulating (MCD) peptide, enzymes, amino acids, sugars and some volatile compounds (Wehbe, *et al.*, 2019).Melittin, the main toxic component, is an oligopeptide composed of 26 amino acid residues. Melittin is a potent inductor of phospholipase A2 (PLA2). The PLA2 catalyze the cleavage of fatty acids and is involved in the release of histamine by polymorphonuclear leukocytes. Several studies have attributed anti-inflammatory, anti-cancer, and anti-viral properties to melittin (Rady *et al.*, 2017., Memariani *et al.*, 2020., Fan *et al.*, 2021).

Adolapin is a polypeptide composedof 103 amino acid residues, it exhibits anti inflammatory properties. These propertiesare attributed to inhibition of the prostaglandin synthetase system (Shkenderov & Koburova, 1982). Apamin isan oligopeptide composed of 18 amino acid residues. Apamin is a neurotoxin that blocks calcium-activated potassium channels (CAPC) (Lazdunski *et al.*, 1986). CAPC are fundamental regulators of neuronal excitability, participating in interspike interval and spike-frequency adaptation. (Vergara *et al.*, 1998). Apamin generates cytotoxic and nociceptive nervous effects (Habermann, 1984). MCD peptide is a cationic small peptide composed of 22 amino acid residues.This compound has a potent neurotoxic action, it causes mast cell degranulation and histamine release at low concentrations (Bidard *et al.*, 1987).The enzymes phospholipase A2 and hyaluronidase have been identified in the bee venom. The PLA2 is a family of enzymes that hydrolyzeglycerophospholipids to produce arachidonic acid as a precursor of eicosanoids, prostaglandins and leukotrienes. PLA2 enzymes are implicated in several biological process such as inflammation and host defense (Murakami& Kudo, 2002). Hyaluronidases are a family of enzymes that hydrolyze hyaluronic acid which is a natural component of joints, cartilage and skin. Hyaluronidases are components of many venoms for instance bee venom and snake venom. This enzyme is considered as a virulence factor that increases the diffusion of venoms and damages the bite site (Gmachl&Kreil, 1993). More than 20 volatile components are present in bee venom.A few examples are isopentyl acetate that is a pheromone that warns bees of danger., and, (Z)-11-eicosen-1-ol that is useful in prolonging the efficacy of isopentyl acetate.The 2-heptatone is within the group of volatile compounds and is known as the provoking factor of aggression among the pheromones of the stings (El Adham *et al.*, 2022).The volatile components of apitoxin includeterpenes, phenolics and alkaloids. These compounds are organic molecules frequently found in plants with secondary metabolite functions (Tomar, 2022b). Secondary metabolites have biological functions that are not essential for plants, for example, they are attractants of pollinating insects or repellents of pests. Terpenes have a molecular base of isoprene a carbon-base compound of 5 carbon atoms. Phenolics have in their structure a molecular base of phenol and several other functional groups that allow them to be subclassified into phenolic acids, stilbenes, lignans, phenolic alcohols, flavonoids, among others. Alkaloids are nitrogenous bases that have an intense physiological action in animals even in low doses. As seen in Figure 1, some phenolic compounds in BV are genistein and apigenin. Procainamide and isonicotinic acid are alkaloids that have also been isolated from apitoxin. Curcumol is the only one terpene isolated from BV.

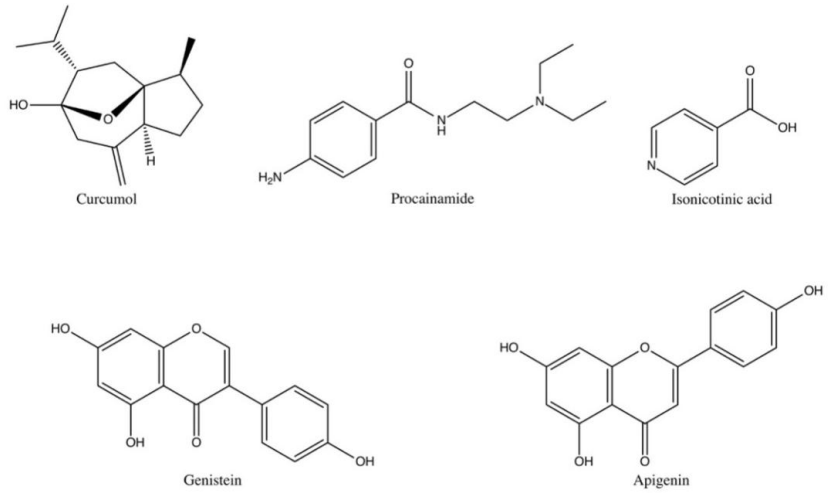

Figure 1.Plant-derived compounds found in bee venom.

Medicinal properties of plant–derived compounds found in bee Venom

Curcumol is a sesquiterpenoid found in *Curcuma* species such as *c. rhizome, c. radhix, c. aromatica*, and *c. weyujin*. Curcumol is part of a family of compounds classified as curcuminoids. Curcuminoids have been extensively studied for their antimicrobial, antioxidant, anti-inflammatory and anticancer properties (Hashem *et al.,* 2021). Hepato-protective activities have been attributed to curcumol. Activated hepatic stellate cells (HSCs) migrate to liver injury sites and secrete extracellular matrix during liver fibrosis. Curcumol is able of inducing necroptosis of HSCs which has been proposed as a major strategy for the treatment of liver fibrosis (Sun *et al*., 2022). Other *in vitro* and *in vivo* studies have reported curcumol effectiveness to treat liver fibrosis and hepatocellular cancer (Huang *et al*., 2022., Zheng *et al*., 2022). In the case of colorectal cancer, several studies have demonstrated the activity of curcumol as an anticancer and antiproliferative agent for renal cell carcinoma cells (Hashem *et al*., 2021).

Procainamide,chemically classified as an alkaloid, is a benzamide-derivative found in medicinal plants (Kim *et al*., 2009).Several alkaloids from the *Cinchona calisaya* plant are used for quinidine production. The quinidine pharmaceutical importance relays on its antimalarial, antiarrhythmic, antimicrobial, anticancer, and antioxidant properties. Quinidine is in high demand, yet its production from the bark of the quina tree is limited., consequently, procainamidewas proposed as an alternative drug to treat cardiac arrhythmias (Rahmawati *et al*., 2021.,Beik *et al*., 2020).Current studies show that procainamide significantly decreases ventricular arrhythmias and therapeutic effects against rhabdomyolysis (Toniolo *et al*., 2021., Shih *et al*., 2016). Besides, procainamide treatment has been proposed as a cardioversion strategy fot the management of atrial fibrillation (Karlsson, 1978., Matuskowitz, *et al*., 2021).The isonicotinic acid is another alkaloid found in apitoxin. The natural sources of this compound include vegetables, fruits, and grains. This compound and nicotinic acid are derivatives of pyridine. The biological properties of nicotinic acid are well characterized in terms of human metabolism as a B-vitamin. Kei *et al*., 2012., Liu *et al*., 2015). Furthermore, isonicotinic acid exhibits important biological activities in the pharmaceutical area. Isonicotinic acid derivatives have been synthesized and fully characterized exhibiting antituberculosis effects (Slivkin*et al*., 2013., Atta *et al*., 2018). The mechanism of action of these compounds is linked to a cell cycle arrest of the infected cells with *mycobacterium tuberculosis* and an induction of apoptosis (Matei *et al*., 2015). Other studies have attributed to isonicotinic acid antibacterial and antiviral properties againstinfluenza virus (Cocking*et al*., 2018., Judge*et al*., 2013).

Genistein is a phenolic compound which is subclassified as an isoflavonoid. This compound is mainly found in medicinal plants and soybeans (Sharifi-Rad *et al*., 2021).Genistein has been extensively studied for its many biological properties to treat diseases such as cancer and neurodegenerative diseases.This isoflavone exerts estrogen-like functions and several preclinical studies have reported antioxidant, anti-inflammatory, antibacterial and antiviral activities (Mukund *et al*., 2017). The molecular effects of genistein play an important role on biochemical pathways including cell proliferation and suppression of tyrosine kinases (Sharifi-Rad *et al*., 2021., Bhat *et al*., 2021).Due to its ability to mimic estrogen, it has been shown to be an effective treatment for endometrial hyperplasia (Yu *et al*., 2021). Apigenin is another plant-derivedflavonoid found in apitoxin. This phenolic is frequently found in fruits and vegetables. Preclinical studies support beneficial effects of apigenin on UV-induced skin damage, vitiligo, dermatitis, wounds, skin aging, and some types of skin cancer (Majma Sanaye *et al*., 2022). This compound mostly acts *via* inhibition of inflammation through suppression of pro-inflammatory cytokines and intracellular inflammatory mediators, as well as antioxidant properties such as improvement of endogenous antioxidant defense mechanisms (Salehi *et al*., 2019). Apigenin induces cell growth arrest and apoptosis in different types of tumors such as breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach, by modulating several signaling pathways (Imran *et al*., 2020).

CONCLUSION

Apitherapy includes all those medical applications of bee products to treat health problems. Bee venom therapy is the branch of apitherapy that uses BV against several illnesses. Bee venom therapy, either topical or intradermal administered, is used to treat skin illnesses such as acne, wrinkles, and wound healing. Besides, this therapy has been used to treat arthritis, pain, and other immune disorders. Apitoxin is mostly water and a low proportion is dry venom, which contains melittin, adolapin, apamin, MCD peptide, enzymes, amino acids, sugars and some volatile compounds. The volatile components of apitoxin include plant-derived compounds such as alkaloids, terpenes, and phenolics. Phenolic compounds in BV are genistein and apigenin. Procainamide and isonicotinic acid are alkaloids that have also been isolated from apitoxin. Curcumol is the only one terpene isolated from BV. Curcuminoids have been extensively studied for their antimicrobial, antioxidant, anti-inflammatory and anticancer properties. Hepato-protective activities have been

attributed to curcumol. Current studies show that procainamide significantly decreases ventricular arrhythmias and exhibits therapeutic effects against rhabdomyolysis. Isonicotinic acid derivatives have been synthesized and fully characterized exhibiting antituberculosis effects. Genistein has been extensively studied for its many biological properties to treat diseases such as cancer and neurodegenerative diseases. Preclinical studies support beneficial effects of apigenin on UV-induced skin damage, vitiligo, dermatitis, wounds, skin aging, and some types of skin cancer.

Conflicts of Interest

The authors declare no conflict of interest.

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