

# Physiotherapeutic treatment with apitoxin: an overview of the worldwide experience

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DOI: 10.29322/IJSRP.8.6.2018.p7805

<http://dx.doi.org/10.29322/IJSRP.8.6.2018.p7805>

**Abstract-** Apitoxin is the venom produced by bees of the genus *Apis*. This toxin is produced by these insects for protecting the hive against predators such as arthropods and vertebrates. Apitoxin is composed by a complex combination of enzymes, peptides and amino acids, as well as small amounts of carbohydrates and lipids. Bee venom and its bioactive compounds have several biological effects against a variety of diseases in humans and animals. The treatment with the bee venom is used in traditional Chinese medicine and since ancient times in Egypt, Greece and India. Nowadays, apitoxin continues to be used in alternative treatment of various diseases such as arthritis, rheumatism, skin diseases, several types of pain and infections, and against cancer. The use of apitoxin has an increasing potential in the pharmaceutical sector, with some products already available. The objective of this research is to outline the physiotherapeutic treatment with apitoxin in the treatment of various diseases, as well as to verify the current status of research in apitherapy.

**Index Terms-** *Apis mellifera*, bee venom, apitoxin, bioactive compounds, arthritis

## I. INTRODUCTION

The attribution of manipulating substances to promote health and curing diseases was intended to the professional pharmacist. The technological and scientific advances of the last years lead pharmacy professionals to new advances in the search for new medicines and the research of the biodynamics of substances used in traditional treatments in order to improve their pharmacological application. The use of this substance has enormous importance to the physiotherapist in the treatment as some articular diseases. Among the traditional treatments, therapy with bee venom presents a great research potential and is a challenge both for professionals of pharmacy and physiotherapy. Toxins produced by venomous animals have substances that can be used in the synthesis of several drug.<sup>1</sup> The animals most investigated in these aspects are: beetles, wasps, ants, grasshoppers, crickets, cockroaches and bees.<sup>2</sup> Bee venom has traditionally been used since ancient times for the treatment of autoimmune diseases such as arthritis and rheumatism, as well as skin diseases and infections.<sup>3</sup> The Greek

physician Hippocrates, considered the father of Western medicine, used bees and their stingers in their medical practices, and the Roman emperor Charlemagne (742-814 d.C.) in the eighth century was treated with bee stings to combat inflammation in the joints.<sup>4</sup> Bee venom treatment has been used by the ancient Egyptians as a homeopathic medicine for the treatment of arthritis and has been used to treat diseases of the immune system, allergic diseases, viruses and inflammatory diseases for at least a millennium.<sup>5</sup>

Based on the review of articles published in different regions of the world, this research have the objective to outline the therapy with apitoxin in the treatment of diseases of physiotherapy interest, as well as to verify the current status of research in apitherapy.

## II. METHODS

It is a research on literature review, carried out through books and scientific articles consulted in physical and electronic libraries such as: Google Scholar, Lilacs, Scielo and PubMed. For data collection, the following descriptors were used: Arthritis, Apitoxin and Immunology. The survey was performed from October 20, 2017 to April 12, 2018. The main target for the eligible texts was the subject, specially the use of apitoxin in joint inflammatory processes and their effects.

## III. DISCUSSION

According to Moreira<sup>6</sup> bees offer totally natural products like honey, royal jelly, wax, apytoxin, pollen, and bee larvae. There are several non-traditional medicine models that also present positive results like acupuncture, phytotherapy, chiropractic, apitherapy, homeopathy and aromatherapy. The author considered apitherapy as alternative medicine which demonstrates an effective method of treatment using apicultural products, such as apitoxin in the treatment of certain human pathologies. This type of therapy was widely used by Native Americans. Bee products represent valuable contributions for the human population as well as for the same animal species, promoting also raw material for health products. There is more research on bees than any other species of insects.<sup>7,8</sup> This assertion was also confirmed by Leite & Rocha when

considering that products of apicultural origin brought important contributions to human civilization, mainly in health and food, and alleges that honey and venom of bee are the most important ones in the area for health. These authors emphasize the importance and tradition of this kind of therapy in the treatment of diseases in humans and animals.<sup>9</sup>

According to Dantas *et al.*, apitoxin is the venom produced by bees belonging to the genus *Apis*, with the purpose of protecting the colony against a diversity of predators, represented mainly by a large number of arthropods and vertebrates. This venom is composed by a complex association of substances like enzymes, peptides and amino acids and also by small amounts of carbohydrates and lipids. Apitoxin and its bioactive compounds have diverse biological efficacy with curative efficacy and in the treatment of a large number of diseases. The therapeutic use of bee venom was already practiced in traditional Chinese medicine, as well as in ancient Greece and Egypt, for the treatment of arthritis, rheumatism and various autoimmune diseases, and in the treatment of neoplasias, skin diseases, pain and infections, and against some lineages of malignant tumors. The use of this toxin has aroused the interest of the scientific community since the nineteenth century and in the 1980s researchers already recognized the importance of its use as a possible therapeutic agent in Western medicine.<sup>10</sup> Nowadays, apitoxin is used as a component of several drugs and have a potential growth in the beekeeping system, which a high visibility and acceptance among the public. Registered pharmaceutical formulas containing raw apitoxin are already marketed on Europe. According to Matysiak *et al.*, the production of apitoxin is presently a parallel activity in beekeeping with significant potential of producing a variety of drugs.<sup>11</sup>

According to the definition of Nogueira-Couto & Couto, apitoxin is a Latin word and means: api=bee and toxin=venom.<sup>12</sup> For many of the bees' small predators, their venom is deadly, even to the bee itself if stung by another of their species. In humans, a sting may be worrying or not depending on the sensitivity of the stung individual and the amount of injected venom.<sup>13</sup>

The bee venom contains bioactive substances with high pharmacological value as analgesic, neurotoxic, vasoactive, hemolytic and cytotoxic actions.<sup>14</sup> The analgesic and anti-inflammatory principles of apitoxin are mainly used in the alternative treatment of arthritis.<sup>15</sup> Among the substances of pharmacological interest, some are enzymes (phospholipase A2 and Hialorunidase) peptides (Melitin, Apamine and Peptide MCD) amines (Histamine, Dopamine and Noradrenaline) carbohydrates and lipids. These compounds, when inoculated in the organism, develop a series of biological reactions in the cell membrane, which vary according to the biochemical diversity of their constituents.<sup>16,17</sup> However, Yasui warns that the composition of apitoxin contains toxic substances, which should be considered in the therapy with bee venom.<sup>18</sup>

One of the most traditional therapeutic uses of the bee venom is in the treatment of rheumatoid arthritis.<sup>15</sup> Rheumatoid

arthritis is a chronic autoimmune systemic disease, which mainly affects synovial joints and other organs such as skin and viscera. The most important characteristic of the disease is a symmetrical polyarthritis and synovitis which typically affects the hands, wrists and feet initially, and subsequently can affect any synovial joint such as knees, ankles, elbows and shoulders. This pathology affects approximately 1% of the human population and with a 3:1 woman-to-man incidence.<sup>19,20</sup> This disease leads to a decrease in the quality of life and labor incapacitation, and women aged between 30 and 50 years are the most affected group.<sup>21,22</sup> According to Azevedo *et al.*, the treatment of rheumatoid arthritis has a high cost for the patient, both financially, with high cost medicaments,, as well as difficult daily activities.<sup>23</sup>

According to Rodés *et al.*<sup>24</sup> and Flores<sup>25</sup>, the treatment of rheumatoid arthritis is limited by the degenerative and inflammatory autoimmune components of the disease. The action of the physiotherapist is limited to resources focused to reducing pain, preventing joint limitation and muscular atrophy and rehabilitation or functionality maintenance. Even with pharmacological therapy for treatment by rheumatology and physiotherapeutic intervention, rheumatoid arthritis often tends to evolve. According to these authors, currently the researchers seek for new therapeutic strategies to allow to control the autoimmune process or at least to reduce inflammation that causes destruction and articular deformity. Among these alternatives, one of the more promising is the apitherapy as a rehabilitation technique. Guimarães & Evangelista commented that within the substances found in nature, the venom produced by the bee *Apis mellifera* is one that contains in its composition peptides and enzymes with potent anti-inflammatory properties. In Brazil, application of apitoxin is little known by health agents. According to these authors, bee venom is used in the city of Beijing, China for the treatment of arthritis, and in the United States of America some pharmaceutical companies manipulate the venom to make medicines for diseases such as multiple sclerosis.<sup>26</sup>

Alternative treatment for various diseases such as arthritis, neuropathies, respiratory and others has been discussed by Moreira<sup>6</sup>. This author considered the form of direct apitherapy, which consists in the practice of direct application of bee stings to the compromised site. In these cases, few stings are necessary, considering that the poison introduced is much more active and should not be applied to allergic persons. The author commented that direct apitherapy is little used in Brazil, especially considering the possible allergic reaction of the patient. In other countries the use of this direct method is very frequent. The author adds that most health professionals and the general population are unaware of this medicinal alternative that has been showing positive results in the treatment of many diseases such as arthritis, in which apitoxin decreases inflammation and pain.<sup>6</sup> Our opinion is that professionals in the pharmaceutical industry conduct intensive researches about the production and application of apitoxin, as well as search for techniques to preserve the stability of its compounds.

Hong *et al.* investigated the effect of bee venom on the treatment of patients with rheumatoid arthritis. They performed

an analysis at the cellular level and demonstrated that apitoxin caused apoptosis of synovial cells after 24 hours from the beginning of the treatment. The authors also observed that apitoxin was responsible for the decrease of the enzyme BCL2 and increased the action of enzymes BAX and CASP3. The results suggest that the toxin inhibits the proliferation of rheumatoid synovial cells by the activation of CASP3 that induces apoptosis.<sup>27</sup>

According to Ali, the use of honey and bee products in the treatment of diseases lasts for hundreds of years. The treatment of diseases using honey is cited in various religious texts including the Veda, the Bible and the Koran. In the traditional therapy with the bee venom is used the injection through stings or needles to treat diseases like arthritis, rheumatoid arthritis, multiple sclerosis, lupus, sciatica, pain in the back, twisting among others. According to the author, the apitoxin contains at least 18 pharmacologically active components including various enzymes, peptides and amines. The researcher believes that sulfur is the main element that induces the release of cortisol by the adrenal glands and so protecting the body against infections. When the patient's body enters in contact with the apitoxin an elaborate a complex cascade of reactions is launched in the body. According to the author, apitoxin is considered as an efficient and safe treatment for human diseases; the average lethal dose (LD50) for an adult person is 2.8mg of venom per pound of body weight. Since each bee injects all its venom and no sting is removed, at most 0.3 mg of venom per stinger, the lethal dose for such a person should be equivalent to 560 stings. For a child weighing 10 kg, something like 93 stings would be fatal. Most people's deaths are the result of one or a few stings due to allergic reactions, heart failure or suffocation from edema that can occur in the neck or mouth. In addition to the accidents that may occur, the authors consider that bee venom is very safe in the treatment of human diseases.<sup>28</sup> Even in cases where the lethal dose is exceeded, the fast attendance is able to stabilize the patient. Azevedo *et al.* reported the case of a patient with acute poisoning syndrome for more than 2000 stings of Africanized honeybees. Early care with hemodynamic stabilization, use of antihypotensive agent, acid-base balance control, urine alkalization, and hemodialysis were efficient to prevent lethality.<sup>29</sup>

The researchers Zaré *et al.* conducted animal studies to investigate the effects of apitoxin as an alternative treatment for arthritis and commented that bee stings were already used in the past as a common treatment of this disease. To investigate the probable beneficial effect of apitoxin on inflammation reduction, the researchers selected 30 Wister rats which were separated into 6 groups. With the exception of the control group, all rats from the other groups were inoculated with 0.5 ml of Freud's adjuvant arthritis inducer. After 9 days of the application, all inoculated animals with the above antigens developed acute joint inflammation, mainly in the knee joint (tibio-tarsal region). The mice in group 2 received no treatment. Group 3 mice were inoculated with saline solution (0.05 ml) subcutaneously at the site of inflammation. Group 4 had cream without apitoxin applied over the lesion. Group 5 was treated with cream containing 200 micrograms of apitoxin/gram of cream. Group 6

was inoculated with a solution of 0.05 ml containing 7 micrograms of apitoxin by subcutaneous injection at the site of inflammation. The parameters determined were: arthritis scale (redness, edema, difficulty of movement) and joint diameter. These parameters were recorded before and after treatment for comparison. According to the authors of the experiment, the results left a great doubt about the use of apitoxin as an anti-inflammatory drug.<sup>30</sup> We believe that treatment with higher doses may be effective against arthritis. The authors of this research induced artificially the inflammation, which may have a different physiological dynamics of natural pathological arthritis.

The researchers Joe-Dong *et al.* studied the effect of apitoxin in rats submitted to arthritis induced by the Freund's method. The research objective was to evaluate the anti-inflammatory effects and anti-cytokine effects of bee toxin on induced collagen type 2 arthritis. The animals treated with apitoxin demonstrated a significantly lower incidence of arthritis when compared to the control group (73% versus 78%). The pro-inflammatory cytokines TNF-alpha production in the treated group was lower when compared to the control group. Histopathological examination of the articulations of the group of rats with arthritis induced of collagen type 2 showed less signs of inflammation and less lymphocyte infiltration after apitherapy. The researchers concluded that acupuncture therapy with bee venom suppressed the development of arthritis and caused inhibition of the immune response in induced arthritis and collagen type 2.<sup>31</sup> This result is the opposed of that the encountered by Zaré *et al.*<sup>30</sup> with a similar experiment.

The treatment of arthritis was also performed by veterinarians in dogs with hip dysplasia. In this research, the activity of caged dogs and the blood cortisol content of normal and arthritic dogs were evaluated before, during and after apitoxin therapy. The treatment result revealed that the motion activity of arthritic dogs increased 70% after a long period of treatment with apitoxin and blood monitoring indicated that the apitoxin used in the treatment stimulated the production of cortisol. This experiment was repeated in another group of dogs, with similar results.<sup>32,33</sup> It was recommended that this study should be understood with caution, considering that extrapolating results from animal models to resolve cases of arthritis in humans. The results also contrast with the conclusions obtained by Zaré *et al.*<sup>30</sup> in animal models.

Beck reported that a group of 108 people who did not respond to treatment with traditional therapy were treated with bee venom, but before the start of treatment each person was tested for possible allergy to the venom. Bee venom was injected twice a week for six weeks. No complications or side effects were observed during treatment, and most patients had improved clinical status at the end of treatment. The author mentioned that bee venom therapy improved the patients' clinical status and provided better living conditions.<sup>32</sup>

Chinese researchers Jae-Hoon *et al.* reported the experience of bee venom treatment in a patient with acute meniscal traumatic injury. The traumatic site was diagnosed by clinical signs and imaging. The researchers injected apitoxin

intramuscularly, prescribed phytotherapeutic medications and monitoring by physiotherapeutic methods. The clinical evolution of the patient was evaluated by the Analogue Visual Scale (AVS). A significant increase in walking time was observed, and the regeneration ratings were evaluated by the Western Ontario and Mc Master Universities (WOMAC) index, and after several treatment sessions the patient showed reduction of pain, walking time and decreased of WOMAC index. Based on these results, the authors affirmed that the intra-articular application of apitoxin was effective in the treatment of the meniscus acute partial lesion.<sup>34</sup>

Joe-Dong *et al.* reviewed the literature on the treatment of arthritis by acupuncture with bee venom. According to these authors the number of studies on the effects of apitoxin and arthritis on animal is sufficient to determine significant anti-inflammatory and analgesic effects. According to these authors there is a lack of studies in humans and it makes premature any conclusion about the efficacy of the treatment. We are of the opinion that rigorous researches with a greater number of patients and adequate design and precautions are necessary to define the efficacy of acupuncture with bee venom in the treatment of human arthritis.<sup>35</sup>

Apitherapy is not regulated in Brazil. In an official opinion, Dr. Stahlke, member of the Medical Council of the Province of Paraná, Brazil was consulted on the authorization of alternative treatments with the use of apitoxin. The adviser understood that the absence of studies of potential risks involved in the application of apitoxin do not allow to recommend the use, even in a complementary way, especially when using the bees directly, since there is no way to guarantee the sterility of the stings, which conflicts with the norms of National Sanitary Surveillance. For the other bee products, the adviser says that there is no scientific evidence of therapeutic action, but they are classified in the category of foods and thus can be consumed by the population.<sup>36</sup> Considering the efficiency of apitherapy already proven by researchers from other countries, we believe that the professionals of the pharmaceutical industry in Brazil intensify research on the therapeutic action of apitoxin, considering that researchers from other countries attest the efficiency of apitherapy for human diseases, particularly in arthritis treatment.

#### IV. CONCLUSIONS

According to the analysis of the world literature review about apitherapy, it is concluded that alternative treatment with apitoxin in patients with inflammatory joint diseases produces analgesic, anti-inflammatory and tissue repair effects, promoting wellness and functional improvement.

Apitherapy requires few resources; it is low cost, and has few side effects. It is a biological therapy that is available to the population with few economic resources, representing an alternative for the high cost treatment of chronic diseases, mainly articular diseases.

Apitoxin, for the diversity of its pharmacological principles, can become an important therapeutic alternative for several diseases and has a potential base for new medicines,

especially for its analgesic and anti-inflammatory properties, providing the return of the patient's well-being quickly.

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