

Nanotechnology mediated bee venom: applications in rheumatoid arthritis

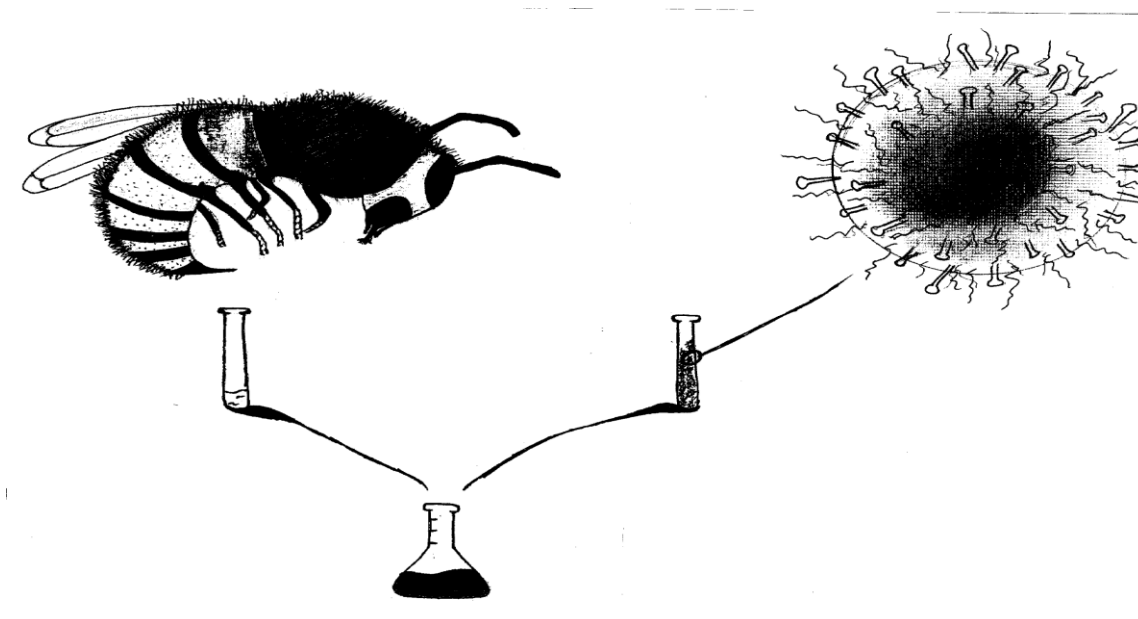
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## Abstract

Bee venom has made medicinal progress, specifically, with the Human Immunodeficiency Virus (HIV) and cancer treatment. However, in spite of this therapy being rooted in the treatment of inflammatory disease, bee venom has made little progress in treating Rheumatoid Arthritis (RA). This substance is both simple and complex in chemical structure, and a few significant obstacles are limiting the effectiveness of the venom in arthritic patients. Primarily, the non-specific cytotoxicity of the venom can negatively affect the surrounding cells of the target, and the known degradation of bee venom, before it reaches the target cells, reduces the potency. One promising way to circumvent these issues would be through nanotechnology. Nanoparticles have a high surface area and, in conjunction with proper functionalization, can be used to derive the Melittin and other beneficial components of bee venom into an effective treatment for Rheumatoid Arthritis. The primary goal of this work is to study contemporary nanoparticles used in drug delivery and do a comparative study on the bee venom and the nanoparticles, helping to develop bee venom into a viable clinical treatment for Rheumatoid Arthritis.

## Graphical Abstract



## Introduction

### **Bee venom composition and applications**

Bee venom therapy has been implemented as a form of treatment for inflammatory disease for many years. It has primarily been injected or delivered naturally to the joints of arthritic patients in regular intervals. It has even been claimed that arthritis and paralysis have been cured with the use of natural bee stings applied in excess [1]. Bee venom is comprised of a number of enzymes and peptides, that make it a powerful substance for damaging or killing harmful cells in the body and increasing blood flow, to reduce inflammation. The primary component of bee venom is Melittin. This peptide makes up 50-60% of the venom and is the main component responsible for the anti-inflammatory effects of bee venom [2]. Other important components of the venom include Phospholipase A2, Apamin, and Mast Cell Degranulating (MCD) peptide, these are found in a lesser amount but can also aid in lessening the symptoms of some common diseases [3]. Although each of these, and many other components of bee venom, can be beneficial in the right amounts, the varying ways that venom has been applied to specific illnesses requires a different function of the bee venom.

### **Bee venom used for the treatment of disease**

The most modern advances in the use of bee venom, as a treatment, have been directed toward HIV and cancer. In the treatment of cancer, bee venom is administered to the tumor cells and in HIV it targets the viral cells in the body. The distinguishing characteristic of RA is inflammation, due to the autoimmune system's attack of the joints in the body. When the autoimmune system is triggered, it activates a host of other cells and functions in the body to react in defense as well [4]. This makes it a slightly different form of treatment than HIV and cancer but the anti-inflammatory effect, along with much experimentation to verify its efficacy,

makes it a viable candidate for the treatment of Arthritis [5]. However, the painful repercussion of being stung by a bee are the result of some negative effects of the venom in the human body. For this reason, there are some obstacles that must be overcome when bee venom is injected as a form of treatment.

### **Bee venom limitations**

Two significant complications associated with bee venom are the non-specific cytotoxicity and the degradation of the venom [6]. These issues primarily relate to how the venom interacts with the body. Bee venom is helpful for its ability to damage or kill target cells in the body. However, the non-specificity of this cytotoxic quality can be dangerous as it could lead to a negative hemolytic effect [7]. The degradation of bee venom is also one of the main issues with direct injection from live bees. The venom will not always make it to target cells of the body as it will dissociate before reaching the tumor, virus, or arthritic joint. One very effective way to overcome these, and other, obstacles of bee venom as a viable treatment could be through the use of nanotechnology.

### **Nanotechnology associated with bee venom**

The use of nanotechnology has only recently been implemented in the delivery of bee venom to target cells, and it has yielded promising results. Nanoparticles are between one and one hundred nanometers in diameter. They have a relatively large surface area, for this size, and functionalization that makes them effective in a variety of disciplines, including drug delivery [6]. The combination of the unexplored aspects of bee venom, and the complications that can be associated with this venom in the body, make nanotechnology a perfect means of drug delivery to develop bee venom into a functional treatment for RA. Knowing that RA is an autoimmune disease can make it difficult to accurately target and deliver the venom to the correct joint

location. Nanoparticles could represent an alternative to the issues of cytotoxicity and degradation by effectively delivering the proper components of the venom, in the proper amount, to the harmful cells at the root of RA.

Although it is clear that bee venom has a powerful affect on the symptoms associated with RA, there have yet to be any medicinal advancements that have developed this substance into a viable treatment. The progress that has been made, utilizing nanoparticles in drug delivery, seems to be a helpful approach for applications of bee venom in the treatment of RA. By comparatively analyzing the modern nanoparticles used in drug delivery, it may be possible to identify the perfect balance that will develop bee venom into a viable treatment for Rheumatoid Arthritis.

### Methods

Nanoparticles have been implemented in a number of scientific disciplines and have even been proven to be effective in drug delivery. Although many medicinal properties, such as bee venom, had previously been abandoned due to a lack of a proper delivery method, through nanoparticle technology many such properties may now be effectively administered to patients. In the case of bee venom, nanoparticles have furthered the effectiveness of the venom in the treatment of other ailments. However, the root of bee venom therapy has been forgotten and RA is still left poorly treated by modern medications. In modern drug delivery techniques, nanoparticles have been synthesized from a variety of materials. These nanoparticles vary in their effectiveness for the delivery of a treatment, based on the form of illness being treated and the drug that is being administered to a patient. By comparatively analyzing which particles have been utilized in the treatment of HIV and cancer, employing bee venom and nanotechnology, it may be possible to determine what can also be applied or altered to treat RA.

Core-shell nanoparticles are composed of two types of metals. One metal (typically hydrophilic) makes up the core and the other (hydrophobic) acts as a shell that allows the core, along with the drug, to make it to the target cell without degrading first. This type of particle is useful in many biomedical applications, but it can be difficult to accurately synthesize. Single metal particles have been more accurately synthesized, and more is known about their efficacy. However, they also have some known complications that could be addressed with the core-shell approach. Depending on which type of metal is used, nanoparticles can be effective as an antibacterial, antimicrobial, or antiviral drug delivery system [8]. Mesoporous Silica Nanoparticles (MSN) are the newest particles being introduced in drug delivery. They have proven to be effective for more precise delivery, with less toxicity to the human body [9]. They also could deliver more of the venom to any given area of the body. Since this is the newest particle in nano research, much is still unknown about how effective it would be in the delivery of bee venom to rheumatic patients.

### Results

With nanotechnology being a relatively new field of research, it can be difficult to hypothesize which type of nanoparticle is best for implementing bee venom therapy as a treatment for rheumatoid arthritis. However, much of the research for nanoparticles is being conducted on cancer treatment. RA is a unique disease in its autoimmunity, and thus the target cells are less specific than that of cancer. This should make experimentation of a variety of nanoparticles the simplest way to determine which would be most effective. For the treatment of RA, nanotechnology mediated bee venom may be the most viable source for an effective modern medication.

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