

Review of: "Anti-metastasis After Bee Venom and Melittin by Upregulation of BRMS1 and DRG1 Genes, With Downregulation of WNT7B in Breast Cancer Cells"

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Potential competing interests: No potential competing interests to declare.

Anti-metastasis After Bee Venom and Melittin by Upregulation of BRMS1 and DRG1 Genes, With Downregulation of WNT7B in Breast Cancer Cells

In the present work, the authors studied the cytotoxicity of whole bee venom, melittin, and cisplatin against two cultured cell lines. Additionally, the down- or upregulation of breast cancer metastasis-related genes was analysed.

My opinion is that the article should be rejected unless some major changes are implemented.

- Overall, the English should be revised. Besides some general grammatical mistakes that are more than understandable, the ideas stated in some sentences are misleading. Clarifying, the overall English is good and understandable, but it could use some minor help.

- Recommended changes/revisions:

Abstract & Introduction

1.- The title is a little bit misleading. Although the down- and upregulation of metastasis-related genes were evaluated after different treatments, no metastasis was studied; only *in vitro* analysis was conducted.

2.- In the abstract, the sentence "*Apitherapy as an alternative medicine is promised to deal with cancer*" is a rather blunt and strong affirmation. Apitherapy as alternative medicine has been reported to have potential beneficial activity, but it has not been implemented in regulated chemotherapeutic treatments. If it has been tested in clinical trials, this should be highly remarked in the text.

3.- In the introduction, "*There are a vast number of studies suggesting the use of bee venom and its major component, melittin, for effective therapy of cancer to deal with uncontrolled cell proliferation and metastable potential.*", these vast numbers of studies should be referenced.

Results & Discussion

1.- One of the main advantages of using MTT for cytotoxicity assays is that it allows us to obtain quantifiable data. Although it is understandable that the authors decided not to show these graphs, I'd highly recommend doing so and

pairing them with the images of cells under treatment.

2.- Figure 1 says Figure 3, please change that. In that matter, the figure's name *Cytotoxic profiles...* could be changed to something else. Again, there's no quantifiable data in the figure, rather a qualitative image, which would be rather good with the other data.

3.- Text mentions that statistical significance was determined for the anti-wound healing properties of the different treatments; nevertheless, Figure 3 doesn't show that. I'd recommend specifying said statistical differences, as well as mentioning what the α value was for the analysis, and not just placing it in the supplementary materials. Even though it is mentioned in the methodology, figures, such as 3 and 5, should specify if the data are means, what the \pm is, and how many replicates were performed.

4.- Up to this point, no differences have been stated between whole bee venom (BV) and melittin. It was indeed previously stated that melittin is the major component of BV, but left there. *Apis mellifera* venom composition has been widely studied, so a study that uses different peptides/proteins should include an SDS-PAGE electrophoresis of the venom or an HPLC chromatogram.

5.- Although the properties of melittin were exposed in this work, more studies are required to demonstrate its potential as an anticancer drug candidate. I'd highly recommend the authors to perform biocompatibility tests, such as hemolytic activity, hemagglutination, and phospholipase activity assays. Considering that BV and melittin have been previously reported as hemolytic agents, and that, alongside melittin, it contains some phospholipases, it'd be interesting, and I believe it'd majorly support the claims of using these types of bioactive components as drug candidates.

It is understandable that some of these suggestions may be out of the main objective or scope of the authors, but I truly believe that they're some major changes that should be implemented for a quality article. In case the authors decide not to implement them, I'd suggest trying to publish it as a communication, rather than an article.

Methodology

1.- The specifics of the equipment used are not mentioned in this section.

2.- In the **cell culture**, the number of seeded cells per well is not mentioned.