Review of: "Inhibition Success of a Virtually Created Molecule: Pseudoeriocitrin and Femtomolar Inhibition"

Federica Maschietto[1]

1 New York University (NYU)

Potential competing interests: No potential competing interests to declare.

The manuscript presents an investigation into the anthelmintic potential of Pseudoeriocitrin, a derivative of the flavonoid glycoside Eriocitrin. While the study's premise and objectives are of clear relevance to global health, there are areas where the manuscript could be enhanced for greater clarity, rigor, and impact. First and foremost, a docking study is absolutely insufficient to prove any of the arguments stated in the study on stability or conformation. The authors should perform a rigorous MD study. I suggest looking at resources like the following: "Making it rain" for a fantastic user-friendly front-end for running molecular dynamics (MD) simulations using the OpenMM toolkit on the Google Colab framework.

Contextualization: The introduction sets a broad stage but could benefit from a tighter focus on the specific gap in the current anthelmintic landscape that this study aims to fill. A clearer articulation of how Pseudoeriocitrin compares to existing treatments could provide a stronger rationale for the study.

Statements such as the following are misleading: "First time a virtual molecule has been shown with femtomolar inhibition constants against several proteins. Hence its interactions with anthelmintic target proteins researched in silico are thoroughly new and original..."

It's important to note that achieving femtomolar inhibition is an extraordinary feat, and most drug discovery efforts yield inhibitors in the nanomolar to micromolar range. The leap from computational prediction to experimental validation is significant, and many factors, including solubility, bioavailability, and off-target effects, play crucial roles in determining a compound's suitability as a drug. According to this study, Pseudoeriocitrin indeed shows femtomolar inhibition constants as predicted by virtual screening. However, such claims require rigorous experimental validation to confirm the computational predictions and establish the compound's therapeutic potential, which I don't believe is provided in this study. The authors should adjust the tone of their claims accordingly.

Methodological Details: The computational methodologies are described with a level of detail that is unnecessary and misleading; however, the presentation of these methods could be streamlined for clarity. Simplifying the technical language and providing a more concise overview of the steps involved might make the methodology more accessible to readers. For instance, generating 3D coordinates from smiles, (no 3D data) is a rather standard practice.

Results Interpretation: The results section presents compelling data on the interactions between Pseudoeriocitrin and target proteins. However, the discussion of these results could be deepened to better articulate the implications of these findings for anthelmintic drug development. Molecular interactions should be confirmed through MD.

As a general remark, I found the reading hard and the writing poor. Many parts could be bettered by using an online editor or seeking revisions through colleagues. For instance, a sentence such as that found in the abstract, "Pseudoeriocitrin is a molecule that does not exist in reality but was created in silicon," is clearly misleading. Below, I provide an improved version of the abstract. I invite the authors to improve the text following similar principles.

Pseudoeriocitrin was created computationally by assuming the formation of oxygen radicals in Eriocitrin and altering its geometry. In-silico docking studies revealed that Pseudoeriocitrin exhibited superior inhibitory activity compared to Eriocitrin, achieving femtomolar results. This study aimed to investigate the underlying reasons for the enhanced inhibitory ability of Pseudoeriocitrin, which is an unusual molecule. The protein-ligand docking method was employed to perform a 3D analysis of potential interactions. Although definitive conclusions are challenging to draw, the absence of hydrogen donors in the structure of Pseudoeriocitrin appeared to make it highly toxic. Conversely, Pseudoeriocitrin formed several hydrogen bonds with atoms in the active site of proteins, which likely contributed to its inhibitory activity. This study represents the first exploration of the structure-activity relationship of Pseudoeriocitrin through in-silico docking. The results demonstrated a correlation between the large core structure, abundance of oxygen atoms, planar coordinates, and femtomolar level inhibition. Further research should be conducted to investigate the chemical properties responsible for these novel biological properties, with particular emphasis on synthesizing non-radical Pseudoeriocitrin.