ASEC 2025 Conference

The 6th International Electronic Conference on Applied Sciences

09–11 December 2025 | Online

MDPI

# Computational Evaluation of Philippine *Vitex negundo* Phytochemicals as Potential Inhibitors of Rhinovirus 3C Protease: Molecular Docking, Pharmacokinetic Analysis, and ADMET Studies

**Francis Ceniza, Harll Fawwenn Hayes Paderanga, Sheena Alexa Yacapin, Nesteve John Agosto**

Department of Chemistry, University of Science and Technology of Southern Philippines, Cagayan de Oro City, 9000, Philippines

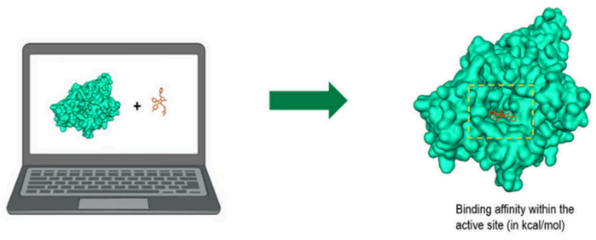
Corresponding Author: nestevejohn.agosto@ustp.edu.ph

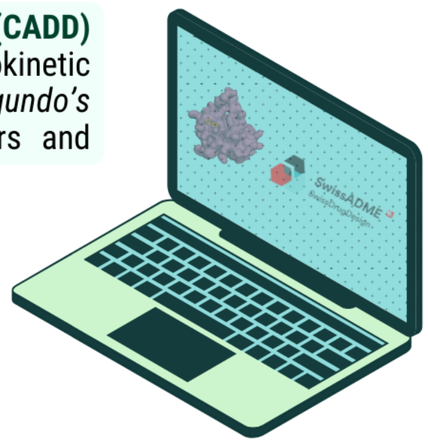
## INTRODUCTION & AIM

The **human rhinovirus (HRV)** is a major cause of common colds, frequently affecting people during rainy seasons. HRVs primary target is the upper respiratory tract causing symptoms like mild fever, cough, runny nose, and fatigue. They replicate by relying on host cells, specifically to its cleaving enzyme, **HRV-3C protease**. To date, no cure or vaccine exists to inhibit this process, and current treatments only relieve symptoms. Thus, searching for viable medicinal treatments, particularly coming from natural sources, is critical.

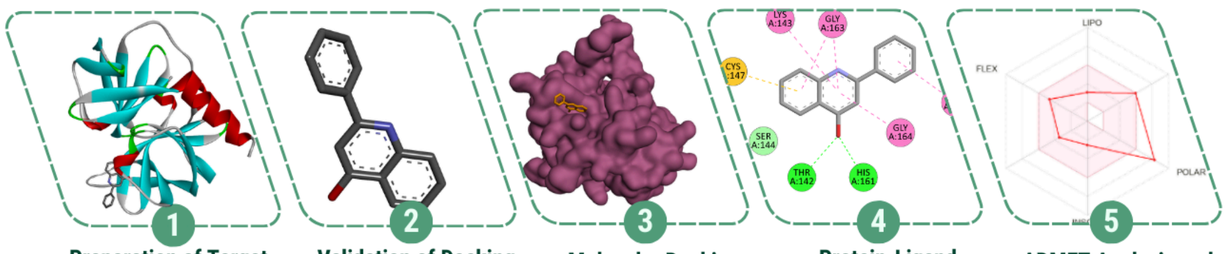
***V. negundo***, locally known as "lagundi", has long been studied as an effective relief medication for inflammatory symptoms associated with common colds or other respiratory infections. With its established anti-inflammatory activity, *V. negundo* is reported to possess potential anti-rhinovirus bioactive compounds or phytochemicals. However, there are still insufficient studies confirming these claims, particularly on evaluating these compounds and their mechanistic actions at the molecular level.

This study utilized **computer-aided drug discovery (CADD)** techniques, including molecular docking and pharmacokinetic ADMET prediction, to evaluate the potential of *V. negundo's* bioactive components as HRV-3C protease inhibitors and assess their viability as drug candidates.

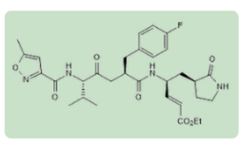



## METHOD




The 3D structure of HRV-3C protease was obtained from RCSB PDB, while the selected *V. negundo* phytochemicals were retrieved from PubChem database or drawn with Biovia Draw 2021. Preparations, optimization, and configurations utilized Avogadro and AutoDockTools.



Rupintrivir, an experimental drug designed to inhibit HRV-3C protease, was utilized as the study's reference inhibitor.

Validation and actual docking simulations were performed using AutoDock Vina, followed by the visualization of their molecular interactions using Discovery Studio Visualizer (DSV).

Finally, drug-likeness and pharmacokinetic analyses were performed on the top performing ligands using online computational tools like SwissADME and pkCSM.

## RESULTS & DISCUSSION

### Validation of Docking Protocol

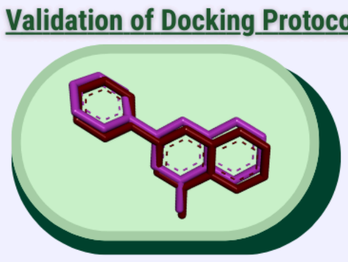


**Figure 1.** Superimposition of the docked and co-crystallized structure of 2-phenylquinolin-4-ol, HRV-3C protease's native ligand. The RMSD value is **0.4262 Å**, (< 2.000 Å), indicating a valid docking protocol.

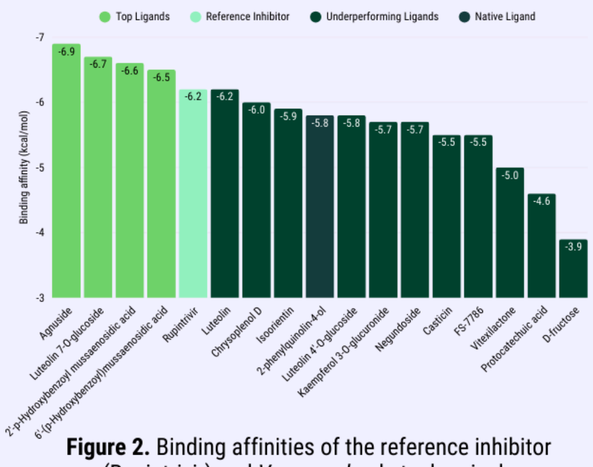



**Figure 2.** Binding affinities of the reference inhibitor (Rupintrivir) and *V. negundo* phytochemicals.

### Protein-Ligand Interactions of the Top Ligands

- Key residues involved include *hydrogen bonds*, *hydrophobic*, and *electrostatic contacts*.
- These interactions support the ligands' strong and stable binding to HRV-3C protease.
- **Agnuside** showed the strongest binding (-6.9 kcal/mol), interacting with Gly 164A and Phe 170A
- Most ligands were bound to His 161A, Thr 142A, and Gly 164A, highlighting the key inhibition areas of the active site.

### Drug-Likeness and ADMET Profiles

- All the top ligands did not comply with Lipinski's Rule of Five, including rupintrivir.
- This correlated in their poor oral bioavailability and GI absorption predictions.

### Molecular Docking Results

***Key findings:***

- Out of 15 *V. negundo* bioactive compounds, only 4 showed superior binding affinity than the reference drug, rupintrivir.
- These "top ligands" may possess the potential to effectively work as HRV-3C protease inhibitors.

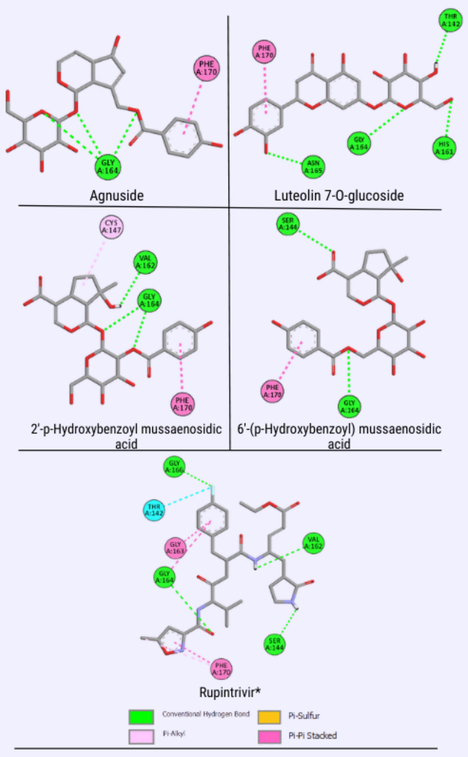



**Figure 3.** Molecular interactions of the reference inhibitor (Rupintrivir) and the top-performing ligands.

Low bioavailability score and non-compliance to Lipinski's Rule of Five can be mediated through drug modification and reformulation in the optimization stages of drug development.

| | 6'-(p-hydroxybenzoyl) mussaenosidic acid | Rupintrivir |
|---|---|---|
| Molecular weight | 496.46 | 598.66 |
| Num. H-bind acceptors | 12 | 9 |
| Num. H-bind donors | 6 | 3 |
| Lipinski's violation | 2 | 2 |
| Bioavailability score | 0.11 | 0.17 |
| GI absorption | Low | Low |
| BBB permeant | No | No |
| P-gp substrate | No | Yes |
| Total clearance (mL/min/kg) | 5.42 | 7.60 |

| | Hepatotoxic | AMES toxicity | CYP Inhibitor 1A2 | 2C19 | 2C9 | 2D6 | 3A4 |
|---|---|---|---|---|---|---|---|
| 6'-(p-hydroxybenzoyl) mussaenosidic acid | No | No | ✗ | ✗ | ✗ | ✗ | ✗ |
| Rupintrivir | Yes | No | ✗ | ✗ | ✗ | ✗ | ✓ |

Only **6'-(p-hydroxybenzoyl) mussaenosidic acid** had a non-toxic yet minimally limiting pharmacokinetic profile, making it the **most suitable candidate** for drug development.

## CONCLUSION/FUTURE WORK

- This in silico study demonstrates that Vitex negundo leaves possess therapeutic potential against human rhinoviruses, particularly through inhibition of HRV-3C protease, addressing the need for effective treatments for HRV-induced respiratory infections.
- The findings suggest that among the selected *V. negundo* phytochemicals, **6'-(p-hydroxybenzoyl) mussaenosidic acid** is the most promising HRV-3C protease inhibitor, especially in terms of favorable ADMET profile–making it a compelling lead compound for anti-rhinovirus drug development.
- For further validation of these results, subjecting 6'-(p-hydroxybenzoyl) mussaenosidic acid and other high-affinity *V. negundo* phytochemicals to in vitro and in vivo assays, is highly recommended to confirm their antiviral efficacy, bioavailability, and safety profiles in controlled conditions.

## REFERENCES:

Scan this QR!

https://sciforum.net/event/ASEC2025