In silico and in vitro models investigating anti-dengue potential of flavonoids from *Carica papaya* leaf juice

Mohd Ridzuan Bin Mohd Abd Razak[1,#], Bee Ping Teh[1,2], Nur Hana Binti Md Jelas[1], Saharuddin Bin Mohamad[2,3,#]

[1]Herbal Medicine Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health Malaysia, 40170 Shah Alam, Selangor Darul Ehsan, Malaysia; tehbp@moh.gov.my, nurhana.mj@moh.gov.my, ridzuan.ar@moh.gov.my
[2]Institute of Biological Sciences, Faculty of Science, Universiti Malaya, 50603 Kuala Lumpur, Malaysia; tehbp@moh.gov.my, saharuddin@um.edu.my
[3]Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), Universiti Malaya, 50603 Kuala Lumpur, Malaysia; saharuddin@um.edu.my
[#]Author contributed equally to the paper

†Presented at 9th International Electronic Conference on Medicinal Chemistry, e-conference, 1–30 November 2023.

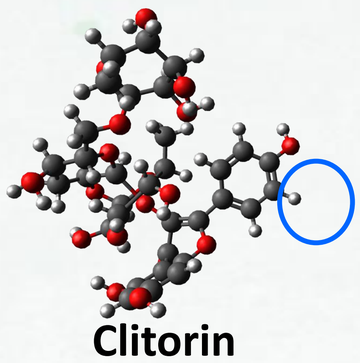
Introduction

Dengue infection has emerged as a significant public health hazard that necessitates global attention, particularly in nations with tropical climates and the dispersal of dengue risk distribution is anticipated to extend to additional countries. This infection represents a pivotal health issue in Malaysia, as underscored by its disconcerting statistical significance. The period spanning from **2009 to 2020 witnessed an excess of 800,000 dengue cases**, accompanied by a **mortality toll surpassing one thousand occurrences**.

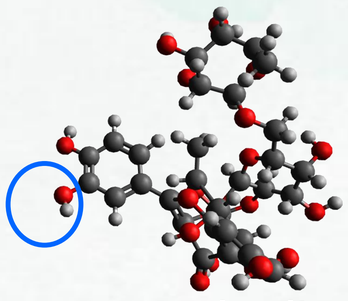
Objective

Therefore, the investigation into the identification of a powerful substance in the treatment of dengue necessitates ongoing development. In this study, **two flavonols (namely clitorin and manghaslin)** identified in the ***Carica papaya* leaf juice** were being assessed their effectiveness in combating dengue through docking simulation and plaque assay.

Methodology



Clitorin (CID: 154701792)



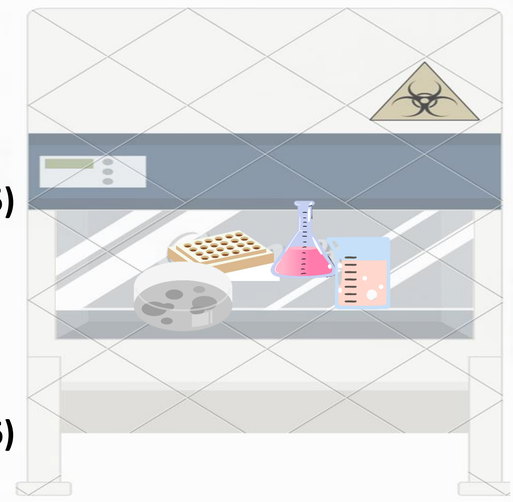
Manghaslin (CID: 14299117)

N2B/NS3 protease (PDB ID: 4M9T)

NS5-RdRp (PDB ID: 5K5M)

Clitorin (CAS: 55804-74-5)

Manghaslin (CAS: 55696-57-6)



AutoDock Tools 1.5.6 software: For preparation of structures
Discovery Studio 2019 Client software: For determination of grid map
AutoDock Vina software: For docking simulation with RMSD of 3.0 Å

DENV-2 New Guinea C strain (ATCC VR-1584): Strain of virus infected on healthy Vero cells

Results & Discussion

- The docking simulation uncovered that the two flavonoids have the potential to bind to the two targeted dengue proteins that are crucial for dengue viral replication. However, it is predicted that manghaslin has a stronger binding interaction with both NS2B/NS3 protease (-8.00 kcal/mol) and NS5-RdRp (-10.70 kcal/mol) than clitorin (NS2B/NS3 protease: -7.90 kcal/mol; NS5-RdRp: -9.70 kcal/mol).
- Utilising the Quest Graph™ IC50 Calculator, the values for the 50% inhibition of virus activity (IC_{50}) from plaque assay were extrapolated. Both compounds that are of interest, namely clitorin (IC_{50} = 0.17 ppm) and manghaslin (IC_{50} = 0.01 ppm), exhibited a superior inhibition of viral activity in comparison to positive control ribavirin (IC_{50} = 147.76 ppm).
- Apart from in vivo research, the results of this study also propose clitorin and manghaslin as potential inhibitors of NS2B/NS3 protease and NS5-RdRp, which should be further explored to determine their drug-like properties, including absorption, distribution, metabolism, and excretion.

ACKNOWLEDGEMENTS

We would like to extend our gratitude to Director General of Health and Deputy Director General (Research and Technical Support), Ministry of Health Malaysia for their support.