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Computational molecular docking of Angiopteroside and its derivatives revealed promising SARS-CoV-2 Mpro inhibitor

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing pandemic that has claimed countless lives and caused significant economic and social disruption in a short span of time. Despite the availability of globally accepted vaccines and supportive treatments, there are still millions of cases worldwide. Moreover, SARS-CoV-2 is a rapidly evolving virus and different variants continue to emerge. Therefore, there is still an urgent need to discover and develop effective inhibitors against the virus. The main protease (Mpro) of SARS-CoV-2 plays a crucial role in the viral life cycle by cleaving polyproteins which makes it a viable drug target. Thus, in this study, twenty-seven (27) proposed compounds, derived from angiopteroside, a delta lactone glycoside isolated from Angiopteris species, were tested against SARS-COV-2 Mpro using in silico method.

Methods

In this research, molecular docking was conducted using different tools such as using AUTODOCK tools 1.5.6., Chem3D 16.0, and Discovery Studios 2021. Angiopteroside and its proposed derivatives were screened for its probabilistic binding with the active site of SARS-CoV-2 Mpro. Additionally, the drug-likeness and ADMET of angiopteroside and its derivative were predicted using PreADMET online server.

Results

The docking results were evaluated based on the free energies of binding (ΔG) and the theoretical inhibition constant (Ki) wherein the angiopteroside derivative with a substituted N-benzyl piperidine moiety exhibited potent binding interaction with SARS-CoV-2 Mpro with a binding energy of -8.32 kcal/mol and Ki of 801.73 nM. These results significantly exceeded the co-crystallized ligand, alpha-ketoamide, which exhibited lower binding energy and Ki of -6.58 kcal/mol and 14.97 µM, respectively. Moreover, the compound satisfied Lipinski's "Rule of Five", predicted to be a non-carcinogen and has excellent cell permeability and intestinal absorption.

Conclusion

In conclusion, the best binding conformation of the N-benzyl piperidine derivative has potent inhibitory activity against SARS-CoV-2 Mpro. This result can give insight to future structure-based studies of agents for the virus. It may be worthwhile to undertake further synthetic design experiments and in vitro/ in vivo evaluation.

Keyword: SARS-CoV-2 Mpro, molecular docking, ADMET prediction