Computational evaluation of the inhibitory potential of phytocompounds from selected African botanicals against human host cell targets of SARS-CoV-2

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Introduction: The coronavirus disease 2019 (COVID-19) is a highly transmissible and pathogenic viral infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It started in Wuhan, China in December 2019 (Madabhavi, et al., 2020). The World Health Organisation (WHO) declared COVID-19 as a global public health emergency on 30 January 2020 and as of 15 December 2021, reported 270 783 891 global cases and 5 312 314 deaths, with South Africa alone recording 90 172 deaths (WHO, 2021). Most of COVID-19 patients present common clinical features such as fatigue, fever, cough, and shortness of breath, while others may remain asymptomatic (CDC, 2020).

Methodology: The X-ray crystal structures of the host targets (hACE2 (PDB ID: 1R4L), TMPRSS2 (PDB ID: 5CE1) and Cat L (PDB ID: 5MQY) were obtained from the RSCB Protein Data Bank (https://www.rcsb.org). Data mining of selected 8 African medicinal plants led to selection of 100 phytocompounds. These compounds were subjected to molecular docking using the AutoDock package on Chimera version 1.14. The compounds with the best docking scores were subjected to Molecular Dynamics Simulation (MDS). Post dynamic analysis of the Hits revealed the leads. Furthermore, binding free energy calculations were done using Molecular Mechanics/GBSA method (Ylilauri and Pentikainen, 2013). The druggability of the leads was predicted by using the online SwissADME tool (Daina etal., 2017)

Results/Discussion: Evaluation of the binding energies of the phytocompounds revealed that abrusoside A (-63.393 kcal/mol) and kaempferol-3-*O*-rutinoside (-58.939 kcal/mol) had strong affinity for the exopeptidase site of hACE2 compared to the reference standard, MLN-4760 (-54.545 kcal/mol). The study further revealed verbascoside (-63.338 kcal/mol), abrectorin (-37.880 kcal/mol), and friedelin (-36.989 kcal/mol) as potential inhibitors of TMPRSS2 compared to nafamostat (-36.186 kcal/mol), while hemiphloin (-41.425 kcal/mol), quercetin- 3-O-rutinoside (-37.257 kcal/mol), and myricetin-3-*O*-galactoside (-36.342 kcal/mol are potential Cathepsin L's inhibitors relative to bafilomycin A1 (-38.180 kcal/mol). The structural analyses suggest that these compounds do not compromise the structural integrity of the proteins, but rather stabilized and established catalytic interactions with the vital amino acid residues crucial to inhibition of the respective proteins.

Conclusion: Overall, the findings from this study are suggestive of the structural mechanism of inhibitory action ofthe identified compounds against the proteins critical to SARS-CoV-2 entry into the host cell. While the study has lent scientific credence to the significant role the compounds could play in the development of potent COVID-19 candidate drugs, further structural refinement and modifications of the compounds for subsequent *in vitro* as well as preclinical and clinical evaluations are underway.

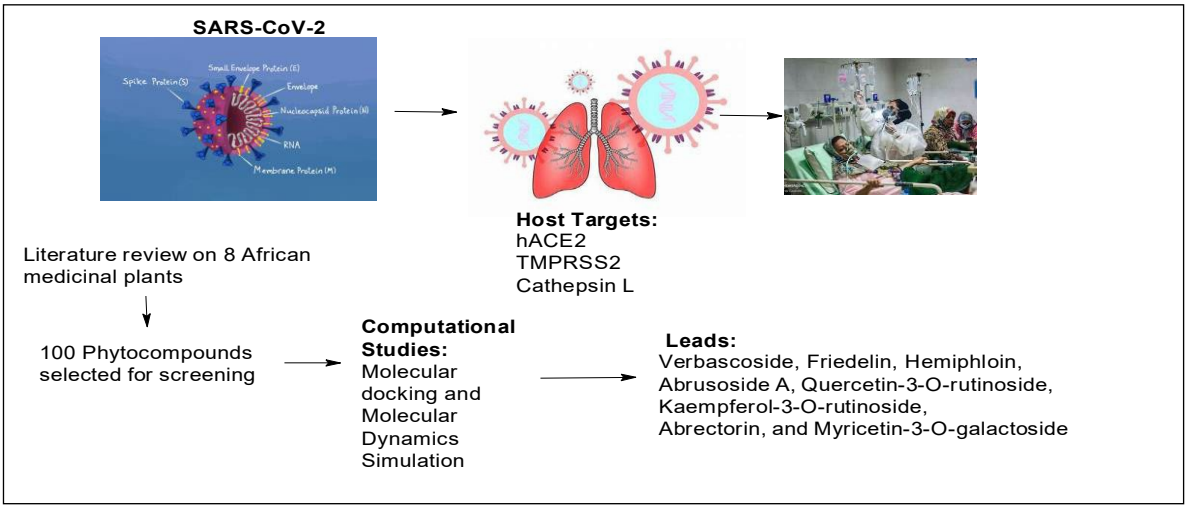

Figure 1*: Schematic summary of the computational evaluation of 100 phytocompounds against COVID-19.*

References:

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