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Allosteric inhibitory actions on Interleukin 6 and Interleukin 1 using selected bioactive compounds to mitigate the cytokine storm; A computational investigation

Rajapaksha RMH[1*], Perera HBT[2], Meepage JN[2], Perera WPRT[3], Dissanayake KGC[4]

[1]Department of Science and Technology, Faculty of Applied Science, Uva Wellassa University, Sri Lanka, [2]Department of Chemistry, University of Kelaniya, Sri Lanka, [3]Research and Publication Division, Gampaha Wickramarachchi Ayurveda Institute, University of Kelaniya, Sri Lanka, [4]Department of Cikitsa, Gampaha Wickramarachchi Ayurveda Institute, University of Kelaniya, Sri Lanka.

Background: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) is spreading vigorously across the world. Patients with severe COVID-19 have a most dangerous condition called a cytokine storm, also recognized as a systematic inflammatory syndrome involving elevated levels of cytokines and immune-cell hyperactivation. To mitigate the cytokine storm of severe COVID-19, Interleukin 6 (IL-6R), and Interleukin 1 (IL-1R) blockers have been proposed as effective drugs. Hence, recognition of the bioactive compounds with proven safety profiles could open a pathway to the development of the most effective drugs against cytokine storm.

Objective: The study intends to investigate the effective phyto-compounds which can be extracted from *Caesalpinia bonduc* and *Ferula foetida* to avoid cytokine storm by inhibiting the IL-6 and IL-1 receptor binding process via *in silico* studies.

Method: Flexible docking was performed for validated IL-1R and IL-6R-α by treating the binding residues flexible with bioactive compounds at possible allosteric sites using AutoDock Vina. As a further analysis, the AMBER 16 program was used to perform 4 ns molecular dynamic (MD) simulation for protein-ligand complexes with the highest binding affinity (BA) to investigate the complex stability.

Results: Among the most concerned bioactive compounds, Taepeenin J had a BA higher than commercial hyperinflammatory drugs (-10.85 kcal/mol) towards IL-1R, with limited oral bioavailability. MD analysis revealed that Taepeenin J may cause conformational movements in IL-1R to discourage the receptor binding process. In addition to that, Nortaepeenin B showed a BA of -8.5 kcal/mol towards IL-6R-α with better oral bioavailability and further MD analysis predicted that conformational movements in IL-6R-α can be induced by Nortaepeenin B.

Conclusion: Based on *in silico* studies, more inspection need to be initiated on the efficacy of bioactive compounds by adhering to the *in vitro* assessments and these computational investigations would open new pathways to focus the attention on drug development against cytokine storm.