Supplementary Materials:

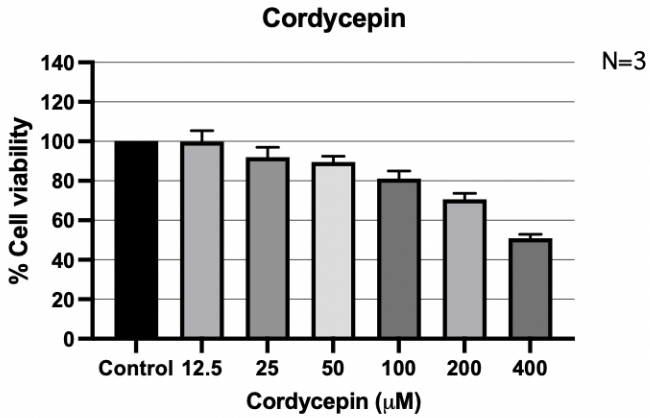

Figure S1. The cell cytotoxicity of cordycepin. The cell viability of Vero cells were measured after 48-hour treatment with cordycepin at various concentrations ranging from 3.125-400 μM by using PrestoBlue ™ reagent (Invitrogen, MA, USA). The data from three experiments were analysed and represented as the % cell viability relative to that of non-treatment control which set as 100%.

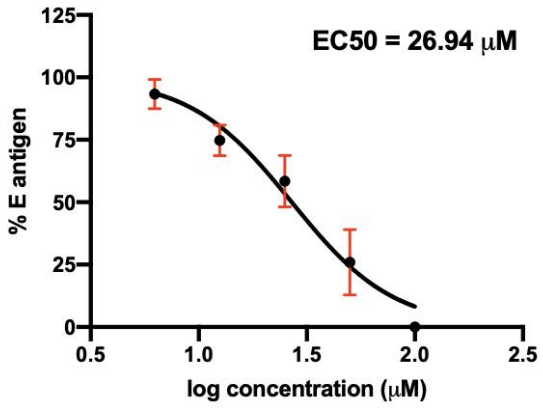

Figure S2. The half maximal effective concentration (EC50) of cordycepin on inhibiting DENV2. The Vero cells were infected with DENV2 and treated with various concentrations of cordycepin. At 48 hours after infection, the cells were harvested and examined the intracellular E antigen by using cell-based ELISA. The data from three experiments were calculated to % E antigen relative to that of non-treatment control (set as 100%). The % E antigen was analyzed for EC50 values by using non-linear regression of GraphPad Prism software version 9.0.2 (GraphPad Software, CA, USA).

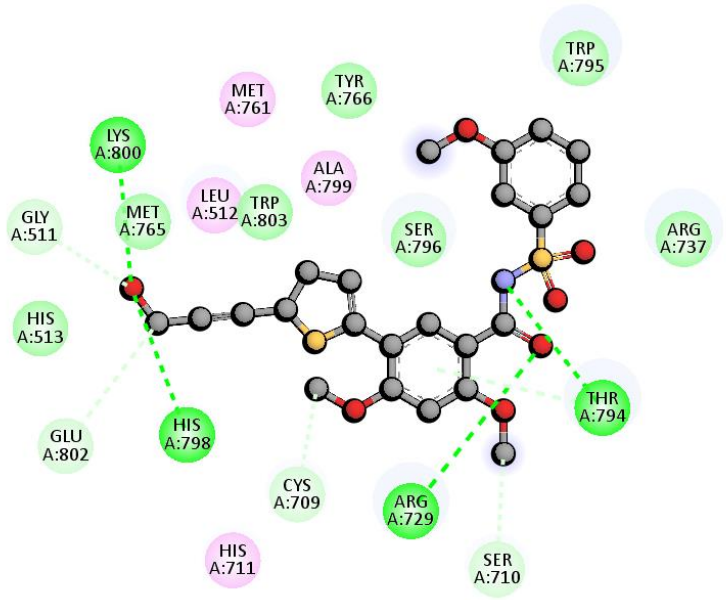

Figure S3. Superpositions of residues in binding pocket of X-ray structure and simulated acyl-sulfonamide derivative bound to the N pocket of DENV2 NS5 RNA dependent RNA polymerase (RdRp)

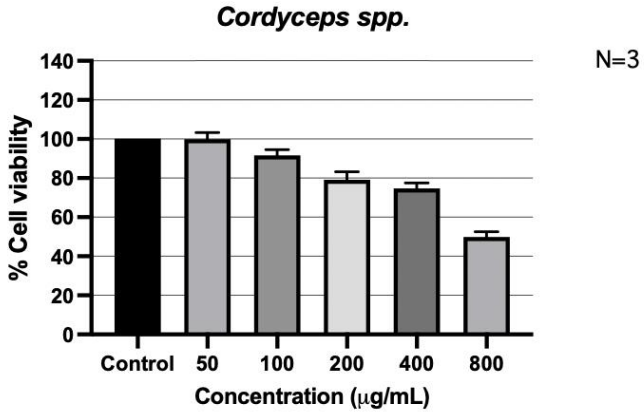

Figure S4. The cell cytotoxicity of *Cordyceps militaris* extract. The cell viability of Vero cells were measured after 48-hour treatment with *C. militaris* at various concentrations ranging from 3.125-400 μM by using PrestoBlue ™ reagent (Invitrogen, MA, USA). The data from three experiments were analysed and represented as the % cell viability relative to that of non-treatment control which set as 100%.

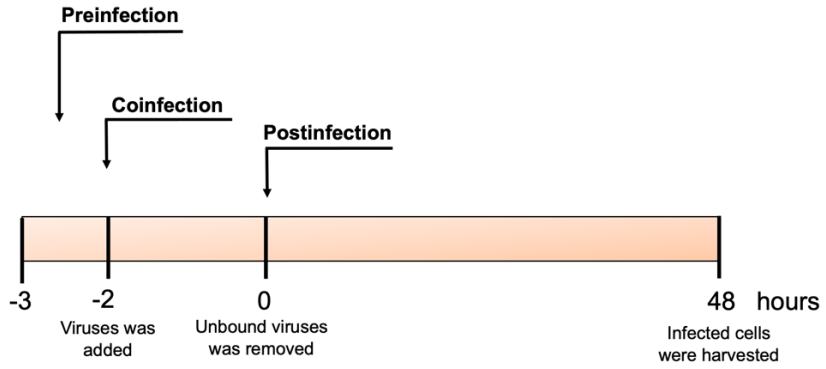

Figure S5. The schematic diagram of time of addition assay. The preinfection step was carried out by adding cordycepin or *C. militaris* extract for 30 minutes, removing, and washing out before infection with 1.0 x 10^4 FFU/mL of DENV2 (100 µL) whereas in the coinfection step, cordycepin or *C. militaris* extract and DENV were simultaneously added. After incubation for 2 hours to allow the virus binding and internalization, the unbound viruses were removed, washed, and added with fresh medium. The postinfection step was performed by cell-virus incubation for 2 hours, addition of cordycepin or *C. militaris* extract and its maintenace along the experiment. The infected cells were harvesred at 48 hours after the infection.