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Abrogating the nsp10–nsp16 switching mechanisms in SARS-CoV-2 by phytochemicals from Withania somnifera: a molecular dynamics study

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Abrogating the nsp10–nsp16 switching mechanisms in SARS-CoV-2 by phytochemicals from Withania somnifera: a molecular dynamics study

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Abstract

The search for therapeutic small molecules and vaccines for Covid-19 treatment is an urgent but evolving topic. The virus has claimed over 3,782,490 lives (as of 12 June 2021), with the figure expected to rise due to the high versatility of the SAR-CoV-2 variant. Therapeutic options based on SARS-CoV-2 inhibitor are essential. Withanolides have a long history in traditional medicines with versatile biological properties including antiviral activities. In this study, the inhibitory potential of withanolides from Withania somnifera (Ashwagandha) against SARS-CoV-2 non-structural protein 10 (nsp10) was investigated by employing atomistic in silico methods viz molecular docking, molecular dynamics and binding free energy calculations. Investigated Withania somnifera compounds demonstrated binding affinity to the nsp10 and in its complex form, that is, nsp10-nsp16 heterodimer. Two withanolides; withanoside IV and withanoside V isolated from the roots of Withania somnifera demonstrated strong inhibition with binding free energies of −29.5 and −29.1 kJ/mol, respectively. Molecular dynamics and binding free energy ascertained the stability of withanoside IV. Water molecules, although known to play an important role in mediating biological systems, herein, water was found to have a repulsive binding effect to some residues, suggesting that the binding of withanoside IV would require dewetting of the nsp10 or displacing the water to bulk solvents. Interestingly, residues in the nsp10 that are responsible for forming stable interaction at the nsp10–nsp16 were found to be strongly interacting with withanoside IV, hence weakening the nsp10–nsp16 interaction and recognition. Further in vitro and in vivo experiments are recommended to validate the anti-SARS-COV-2 potential of these phytochemicals.

Keywords

SARS-COV-2; COVID-19; Withania somnifera; Molecular dynamics; Natural products