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Molecular insights into the *in silico* discovery of corilagin from *Terminalia chebula* as a potential dual inhibitor of SARS-CoV-2 structural proteins

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ABSTRACT

The spike (S) glycoprotein and nucleocapsid (N) proteins are the crucial pathogenic proteins of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) virus during its interaction with the host. Even FDA-approved drugs like dexamethasone and grazoprevir are not able to curb the viral progression inside the host and are reported with adverse effects on body metabolism. In this context, we aim to report corilagin a novel, potential dual inhibitor of S and N proteins from *Terminalia chebula*. The bioactive compounds of *T. chebula* were subjected to a series of computational investigations including molecular docking simulations, molecular dynamics (MD) simulations, binding free energy calculations, and PASS pharmacological analysis. The results obtained from these studies revealed that corilagin was highly interactive with the S (-8.9 kcal/mol) and N (-9.2 kcal/mol) proteins, thereby showing dual inhibition activity. It was also found to be stable enough to induce biological activity inside the inhibitor binding pocket of the target enzymes throughout the dynamics simulation run for 100 ns. This is also confirmed by the changes in the protein conformations, evaluated using free energy landscapes. Outcomes from this investigation identify corilagin as the lead potential dual inhibitor of S and N proteins of SARS-CoV-2, which could be taken for biological studies in near future.

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) is a single-stranded RNA virus of the family Coronaviridae, which infects a wide range of hosts causing severe acute respiratory syndrome (SARS) (Kumari et al., 2020; Patil et al., 2020a). Several research groups from various countries have studied the genome and amino acid sequences of COVID-19. The sequenced viral genome revealed the presence of specific structural proteins, such as spike glycoprotein (S), membrane (M), envelope (E), and nucleocapsid (N), that are linked with the robust viral progression in the host. These proteins are mainly involved in the host cell infection and thus, should be targeted for further screening and the development of potential drugs or medications against COVID-19 (Patil et al., 2020b; Patil et al., 2020c).

Among the 4 structural proteins of the SARS-CoV-2, S and N proteins are extensively studied. This is due to their extensive genomic variations that are responsible for their structural modifications over time, hence the pathogenicity (Patil et al., 2021a). In a genomic pathogenicity determination test, N protein was found to be the most enriched, followed by the S glycoprotein. Also, the polyprotein 1ab and membrane glycoprotein were not significantly enriched with such differences (Gussow et al., 2020). Antibody response was also found to be more towards these 2 proteins (Fenwick et al., 2021; Mariën et al., 2021). Since both the proteins evoke extensive antibody response compared to other targets, S and N proteins could act as potential drug targets to curb the viral progression inside the host body.

Several studies have exploited the role of computational tools in assessing the possible drug targets for the development of treatment (Patil & Ramu, 2020a; Patil & Ramu, 2020b).

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