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Structure-Based Design and Molecular Simulations of Some Quercetin-Based Drugs as Repurposable Inhibitors of SARS-CoV-2 Main Protease

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Abstract

In this study, virtual screening and molecular dynamics (MD) protocols were applied to screen 2826 FDA-approved natural product drugs from the Selleckchem.com library for prospective inhibitors of the SARS-CoV-2 main protease. From the virtual screening through HTVS, SP and XP docking analysis, hyperoside, rutin hydrate, rutoside and quercitrin displayed a stronger binding affinity with respective XP docking scores of –11.389, –11.340, –11.087 and –10.232 kcal/mol than co-crystallized N-[2-(5-fluoro-1H-indol-3-yl)ethyl]acetamide (HWH) and positive inhibitors, lopinavir and ritonavir which scored –5.493, –6.463 and –6.221 kcal/mol respectively. Selectively, the binding free energy, MMGB(SA) of hyperoside and rutin hydrate was observed as –21.55 and –25.82 kcal/mol respectively compared to lopinavir and ritonavir with –17.66 and –5.28 kcal/mol respectively. Consistently, the selected drugs displayed good thermodynamics conformational stability, thus, recommended as promising repurposable inhibitors of the SARS-CoV-2 main protease amenable for further studies.

Keywords: SARS-CoV-2 main protease, Molecular docking, Molecular dynamics, Quercetin, Natural repurposable drugs

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) suddenly emerged around late 2019, thereby causing a global pandemic termed coronavirus 2019 (COVID-19). Since its zoonotic outbreak similar to the previous SARS-CoV-1 and Middle East respiratory syndrome CoV (MERS-CoV), it has destabilized global healthcare and economic systems through daily infections and loss of lives [1,2]. Although, the evolution of various vaccines has significantly doused the tensions of COVID-19 infection worldwide, however, there remains a challenge of accessibility to address the urgent situations, making a continuous search for effective therapeutics remain significant.

The viral main proteases (M^{pro}) of SARS-CoV-2 play pivotal roles in the modulation of viral life processes such as replication and transcription. The enzymes are strongly implicated in the proteolytic cleavage of viral polyproteins such as the pp1a and pp1b into intermediates or fully developed viral proteins including the nsp4-9 and nsp12-15, as such, representing plausible therapeutic targets [1,3,4]. Notably among the inhibitors of the target in clinical applications of COVID-19 include lopinavir and ritonavir, however, they are reportedly challenged by short-term efficacy, inability to reduce mortality and various degrees of aftereffects [5]. These make the continuous search for better alternatives remains important.

The scientific processes in modern drug design are cost-effectively managed and accelerated with the aid of computational molecular modelling, strategically, through ligand-based or structure-based design [6]. Molecular docking and molecular dynamics remain some of the most popular structure-based computational tools for an augmented and accelerated study of characteristic binding interactions of bioactive molecules to therapeutic targets as well as stability. Among the high-performance strategies, the workflow of high throughput screening integrates stratified ligand-receptor docking protocols, from high