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Epicatechin is a promising novel inhibitor of SARS-CoV-2 entry by disrupting interactions between angiotensin-converting enzyme type 2 and the viral receptor binding domain: A computational/simulation study

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Highlights

- The inhibitory activity of 3663 ligands' conformers from sixty-six sources of Iraqi medicinal plants was investigated.
- The screening of all ligands to the targeted ACE2 receptor showed that the epicatechin from *Hypericum perforatum* can bind ACE2 excellently.
- The desirable pharmacokinetic and druglikeness properties and the absence of any possible toxicity have prevailed epicatechin over the other screened compounds. A.
- The stable binding capacity to ACE2 and a high-quality MD profile have confirmed its superiority over other compounds.
- Epicatechin could act as a potential inhibitory agent to prevent the binding of ACE2 with the SARS-CoV2 spike.

Abstract

Angiotensin-converting enzyme 2 (ACE2) is the first target of SARS-CoV-2 and a key functional host receptor through which this virus hooks into and infects human cells. The necessity to block this receptor is one of the essential means to prevent the outbreak of COVID-19. This study was conducted to determine the most eligible natural compound to suppress ACE2 to counterfeit its interaction with the viral infection. To do this, the most known compounds of sixty-six Iraqi medicinal plants were generated and retrieved from PubChem database. After preparing a library for Iraqi medicinal plants, 3663 unique ligands' conformers were docked to ACE2 using the GLIDE tool. Results found that twenty-three compounds exhibited the highest binding affinity with ACE2. The druglikeness and toxicity potentials of these compounds were evaluated using SwissADME and Protox servers respectively. Out of these virtually screened twenty-three compounds, epicatechin and kempferol were predicted to exert the highest druglikeness and lowest toxicity potentials. Extended Molecular dynamics (MD) simulations showed that ACE2-epicatechin complex exhibited a slightly higher binding stability than ACE2-kempferol complex. In addition to the well-known ACE2 inhibitors that were identified in previous studies, this study revealed for the first time that epicatechin from *Hypericum perforatum* provided a better static and dynamic inhibition for ACE2 with highly favourable pharmacokinetic properties than the other known ACE2 inhibiting compounds. This study entailed the ability of epicatechin to be used as a potent natural inhibitor that can be used to block or at least weaken the SARS-

CoV-2 entry and its subsequent invasion. *In vitro* experiments are required to validate epicatechin effectiveness against the activity of the human ACE2 receptor.

Previous Next

Keywords

ACE2; COVID-19; Drug design; Epicatechin; Medicinal plants; SARS-CoV-2

1. Introduction

The Angiotensin-converting enzyme 2 (ACE2) protein, is one of the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases. It plays a crucial role in the pathogenesis of SARS-CoV-2, as it provides a route of entry of viral particles, establishing it as a functional receptor for this newly emerged outbreak [1]. This protein is encoded by the *ACE2* gene, which has recently attracted high scientific attention since emerging of the viral pandemic. The *ACE2* gene is positioned on chromosome X, within the Xp22.2 arm. It consists of 19 exons, with an open reading frame encoding up to 805 amino acids. The mature product of the ACE2 protein has a molecular weight of 110–120 KD [2]. It is well-established that ACE2 protein contains an extracellular domain (starting from the first to 740 amino acid residues), a transmembrane region (741–768 amino acid residues), and an intracellular tail (769–805 amino acid residues) [3].

SARS-CoV-2 particles attach and enter the host cells through the binding of the receptor-binding domain (RBD) of the spike (S) proteins with the ectodomain portion of ACE2 [4]. This sort of direct interaction between SARS-CoV-2 and ACE2 is thought to be the key essence of the efficient spread of this viral infection among humans [[5], [6], [7]]. Based on the interaction of the viral RBD with the host ACE2 receptor, small compounds can be utilized to target the rapid proliferation of the virus through inhibiting its cognate receptor. Once the host ACE2 is being occupied by these compounds, the viral RBD loses its attachment to this receptor before entering inside the host cell. Once the ACE2 receptor is blocked, it would be more difficult for SARS-CoV-2 to gain access to the host cells, which could at least slow the onset of the epidemic until the invading virus disappears [8]. Since the binging affinity of the newly emerged SARS-CoV-2 is 10–20 folds stronger than that SARS-CoV to the host ACE2 [9], the inhibition of ACE2 is one of the best regimens to prevent the outbreak of these newly emerged viral particles. Thus, blocking this receptor may be effective in preventing this highly emerged viral particle from entering the cell and performing its scheduled role of infection.

COVID-19 is currently being treated with some anti-infective drugs, such as antiviral drugs [10], antimalarial drugs [11], and immunosuppressive drugs [12]. However, the effectiveness of these drugs in treating patients with SARS-CoV-2 has not been approved yet [13]. Several synthetic compounds have recently been suggested to inhibit ACE2 by binding with the amino acid residues that are involved in direct interaction with the viral receptor-binding domain (RBD). However, it is well-known that each suggested synthetic may take several years of validation before its become commercially available [14]. Alternatively, several natural compounds have recently been suggested to inhibit ACE2, such as flavonoids [15], proanthocyanidins [16], secoiridoids [17], xanthones [18]. These natural compounds of have high biological availability and low cytotoxicity are the most recommended for the possible treatment of SARS-CoV-2 patients [19]. Given the importance of natural compounds for inhibiting ACE2, several pieces of research have been conducted to prevent the binding of ACE2 with RBD using many natural compounds derived from a variety of plants around the world, such as the flavonoid isothymol from *Ammoides verticillata* [20], the steroid glycyrrhizin from *Glycyrrhiza glabra* [21], the alkaloid nicotianamine from soybean [22], the phytocompound withanone from Indian ginseng (*Withania somnifera*) [23], resveratrol from grape skins (*Vitis vinifera*) [24], and the quinolone rilapladib from *Diplocyclos palmatus* [25]. However, further investigations of other medicinal plants resources in other portions of the world are rather important to confirm these findings and to find out the most eligible compound to inhibit this receptor. Therefore, this study has been conducted to find out natural alternative agents for preventing ACE2 from direct binding with SARS-CoV-2 with more eligible physiochemical properties and better oral bioavailability.

2. Materials and methods

2.1. Study design

Both protein and ligands were retrieved, prepared, and docked. The investigated compounds with the highest docking scores with the ACE2 receptor were further screened via several druglikeness and toxicity predictions. The best-suited compounds in terms of high docking scores, favourable druglikeness properties, and absence of toxicity were analyzed by further docking and MD simulation to find out the best natural compound for the ACE2 receptor. A schematic diagram detailing the main tools employed in the study is shown in Fig. 1.