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Research Article

Molecular docking of some plants acts to inhibit angiotensin-converting enzymes and interaction between spike protein of SARS-CoV-2

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It is shown that new inhibitors will likely need to be discovered in order to slow and eventually eradicate the pandemic. We attempted to provide a brief overview of the novel coronavirus (SARS-CoV-2) and its control through the use of safe, natural active substances in order to enhance comprehension of the COVID-19 pathway. There is a dearth of information on the potential use of stable medication docking to viral illness management. There are currently no COVID-19 vaccinations or efficient medications on the market. Notwithstanding the significant rise in deaths at older ages among patients with diabetes and hypertension, scientists worldwide are still searching for a viable solution for COVID-19. Recently molecular docking was used to design drugs and reduce the time and cost to give a result near clinical trials on patients. It was widely known in the early stages of the pandemic that individuals with severe COVID-19 infections had marked immunological dysregulation, including lymphopenia and elevated expression of inflammatory mediators. T-cell activation is elevated in patients with severe acute COVID-19 infection, and T-cell fatigue follows. This significant and long-lasting decline in functional T-cells occurred after the acute infection. Numerous research has shown that reduced levels of antioxidants in the serum are linked to worse results, the majority of cases linked antioxidant deficiency to high inflammatory factors, high mortality, acute respiratory distress syndrome, cardiac injury, acute kidney injury, thrombosis, and the need for mechanical ventilation (MV). It appears that patients with COVID-19 may benefit from higher antioxidant levels to stop the disease from progressing.

Keywords: *coronavirus, angiotensin converting enzyme, glycyrrhizin, molecular docking*

Introduction

A family of similar RNA viruses known as coronaviruses is responsible for illnesses in both birds and mammals. They can result in respiratory tract infections that are fatal or minor in both people and birds. Some occurrences of the common cold, which are also caused by other viruses, primarily rhinoviruses, are considered mild infections in humans, whereas more deadly viruses can cause SARS, MERS, and COVID-19. They induce diarrhea in pigs and cows, encephalomye and hepatitis colitis in mice (Singhal, 2020). The hosts of coronaviruses (CoV) are diverse and include a wide variety of animal and avian species. They are members of the virus family whose genetic information is encased in positive-sense RNA. The initial cases were connected to a sizable Wuhan seafood and livestock market, where the real pneumonia first appeared. The current 2019-nCoV cases of acute respiratory sickness were reported in a number of Asia countries; all of these people had traveled to Wuhan City before the rapid development of this event. On January 10, 2020, the genome (WH-Human_1) in Wuhan CoV sequence was first made public Five sequences of Wuhan CoV genome were then made public (Zhou et al., 2020; Shu & McCauley, 2017)**.** Compared to MERS-CoV, the genome (WH-human-1) displays huge

sequence homology to the genomes (SARS-CoV). Consequently, researchers suggest that 2019-nCoV can be effectively associated with human ACE2 molecules by the use of S-protein structure modeling (Xu et al., 2020). In addition to ACE2 was first identified in the kidney, testis, and heart. With its active site domain exposed to the extracellular surface of endothelial cells and the renal tubular epithelium, ACE2 is a type I integral membrane protein (Choudhry et al., 2020). Since ACE2 separates the angiotensin I and angiotensin II vasoconstrictor, it acts as a counterweight to the metabolization of blood peptides, which may necessitate the renin-angiotensin system (RAS) to stabilize the ACE products. Specifically, ACE2 has been associated with regulating the ratio of angiotensin II due to that act as hypotensive, as well as angiotensin-(1–7) in the regulation of renal and cardiac function (Bhagat et al., 2022).

According to Metz et al. (2024) noted that ACE2 receptors for the pathogenesis of COVID-19 disease. As a consequence, it has been reported that the 2019-nCoV receptor can enter expressing cells of human ACE2, but not enter to other receptors. Furthermore, it has been reported that human ACE2 is the receptor of the newly evolving 2019-nCoV receptor (Letko et al., 2020), Since the human host cell's receptor is necessary for the virus's entry via blocking ACE2 helps so that 2019-nCoV the spread of infection. It can take a while to develop and manufacture new medications that target ACE2 and treat 2019-Cov (Kaur et al., 2023). Thus, as the infection steadily worsens, it seems impossible to develop and evaluate the compatibility, safety, and toxicity of new treatments in such a short amount of time (Randeepraj et al., 2020) .

Based on their availability and mild toxicity, active agents from Asian herbal medicine may be screened to target (ACE2 receptor) as a potential therapy strategy for 2019-nCov. Crucially, we provide an overview of the efficacy of natural substances that ACE2 may target in order to potentially cure 2019-nCoV. In this succinct analysis Consequently, we suggest potential drugs utilizing molecular docking that bind to the ACE2 receptor and have antiviral properties to stop 2019-CoV infection, such as baicalin, scutellarin, hesperetin, glycyrrhizin, and nicotianamine (Figure 1).

The angiotensin-converting enzyme and its receptor 2 (ACE2)

ACE2 is an enzyme that is attached to the membranes of the heart, kidney, lungs, arteries, and intestinal cells. It lowers blood pressure by catalyzing the conversion of angiotensin II, a vasoconstrictor peptide, into angiotensin 1–7, a vasodilator. Conversely, ACE2 inhibits the activity of the related ACE enzyme by raising Ang (1–7) and decreasing angiotensin-II, which creates a potential target for medication treatment of cardiovascular diseases. Furthermore, ACE2 serves as a portal for numerous coronaviruses, such as extreme acute respiratory syndrome, to enter cells (Randeepraj et al., 2020). SARS-CoV and COVID-19 are two examples of coronaviruses that use ACE2 as a transmembrane protein as their primary portal of entrance into cells. More significantly, endocytosis and translocation of the virus and enzyme into cell endosomes are caused by the binding of (SARS-CoV-2 and SARS-CoV spike S1 proteins to the ACE2 receptor on the cell surface (Organization, 2020). In addition, the host serine protease TMPRSS2 activates the S protein during this entrance phase. This activation is being investigated as a potential therapeutic inhibitor, which has led some to speculate that lowering ACE2 levels in cells may aid in the battle against the infection). On the other aspect, ACE2 has been demonstrated to play a saving role versus virus-induced pulmonary damage by raising vasodilator angiotensin synthesis (1–7).

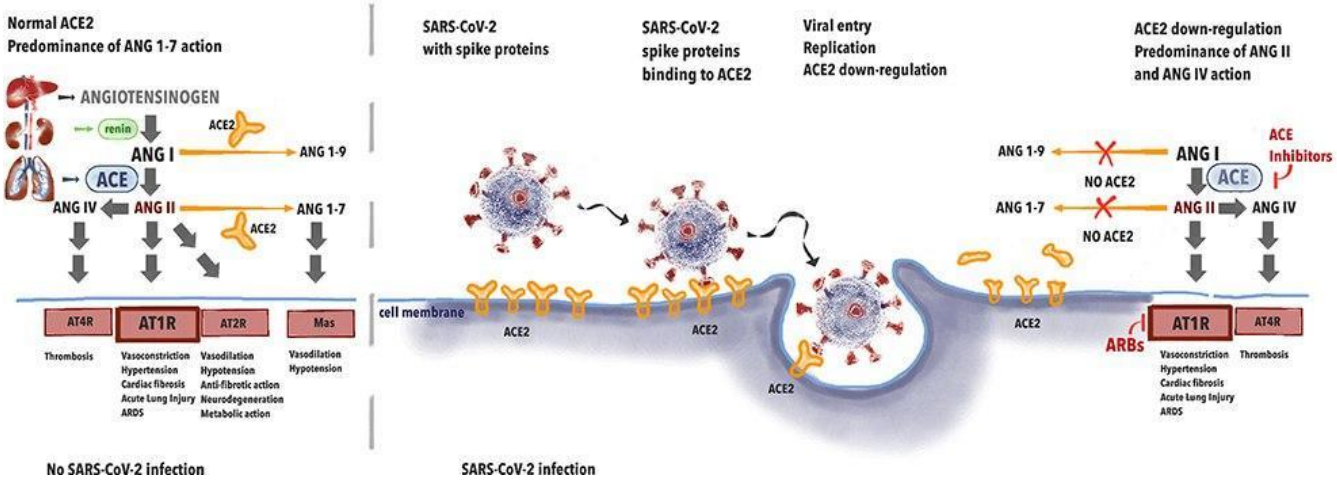

Figure 1. Angiotensin 1 and ACE2 pathway in blood pressure and inflammation regulation (Sieńko et al., 2020).

Materials and Methods

Ligand determination

Our and other researchers' earlier in vitro and in silico tests on the antiviral movement of plant-derived compounds served as the premise for the choice of these compounds as ligands within the docking prepare in this think about. The data was found by looking an advanced library.

These compounds were Anthocyanin, Epigallocatechin-3-gallate, baicalin and Hesperetin (Lin et al., 2024).

Determination of Receptors

Two SARS-CoV-2 proteins were chosen as medicate disclosure targets: primary protease (Mpro) (too called 3C-like protease- 3CLpro) (PDB code: 6LU7) and spike glycoprotein (S) (PDB code: ACE2 through binding citations (ARG-559, GLN-388, ARG-393, and ASP-30).

Results

This study has indicated the role played by some plants or their extracts in inhibiting the enzymes responsible for the entry of the virus, thus curbing its influence inside the body and cutting off the main pathways of its life cycle, in addition to its high effectiveness in supporting the body's immune defenses to confront the virus through its content of effective substances that kill and inhibit on the one hand and strengthen the body's immunity on the other hand. This study confirmed the ability to inhibit ACE that responsible for many pathways like virus entry and hypertension. The present study noted that IC50 or % inhibition (mg/ml) of ACEI was more potent in qurecusin, cinnamoomumzely and berberine Figure (2), while Anthocyanin 5,3'-aromatic acyltransferase H174A refer to the active site and affinity of binding between target and receptors figure (3).

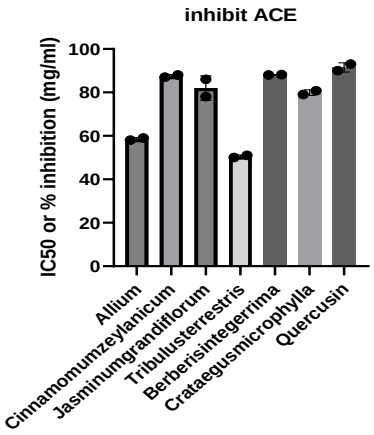

Figure 2. IC50 or % inhibition (mg/ml) of ACEI for some plant

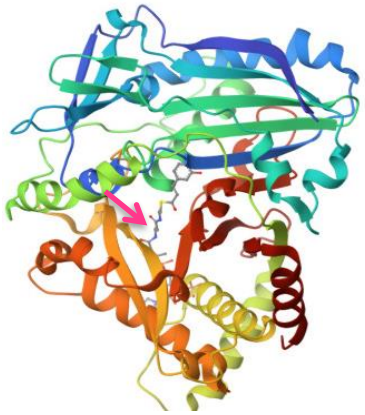

Figure 3. Crystal Structures of Anthocyanin 5,3'-aromatic acyltransferase H174A mutant with caffeoyl-CoA, the arrow noted refer to active site and affinity of binding between target and receptors.

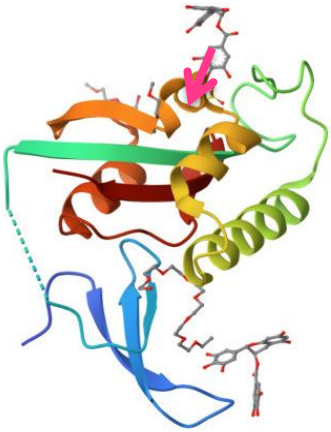

Figure 4. Structural and functional insights of directly targeting Pin1 by Epigallocatechin-3-gallate, the arrow noted refer to the active site and affinity of binding between target and receptors

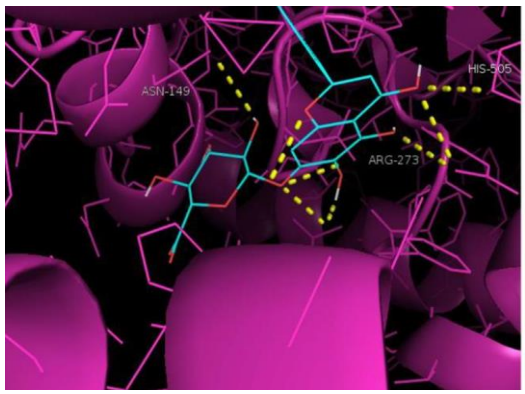

Figure 5. The appear molecular docking data confirmed by (Chen and Du, 2020) on binding of baicalin with ACE2 enzyme

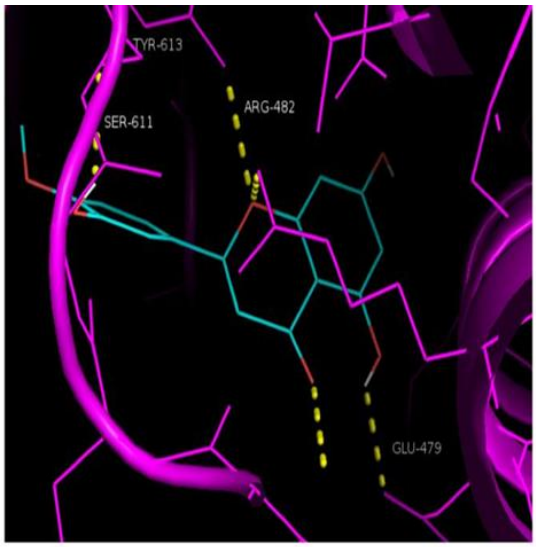

Figure 6. Chemical interaction of Hesperetin to ACE2 enzyme using molecular docking technique

Discussion

Crude extracts are typically used in in-vitro and/or in-vivo assays as part of natural product-based drug discovery initiatives in developing nations. Few attempts have been made to isolate active principles for studies aimed at elucidating structure. Evaluations of bioactivity are scarce in studies that separate pure secondary metabolites and describe their

structures. Molecular docking is a helpful technique in traditional drug discovery programs that helps predict how small molecules will interact with drug targets to inform synthesis choices.

Following the SARS outbreak in 2003, scientists started looking into the function of glycyrrhizin in defense against SARS-associated coronavirus (SARS-CoV) infection. The antiviral effects of five medications, including glycyrrhizin and ribavirin, were assessed by Cinatl et al. (2003) on SARS-CoV. It was discovered that glycyrrhizin had the greatest inhibitory effect on SARS-CoV replication in Vero cells. Glycyrrhizin, a naturally occurring chemical found in Asian herbs such as licorice root (Glycyrrhiza radix), has been identified as potentially useful in reducing the transmission of SARS (Ng et al., 2021). Glycyrrhizin is used to treat chronic hepatitis since it is generally non-toxic. In a lab experiment (Huan et al., 2021). The complete genome sequences of SARS-CoV-2 and SARS-CoV exhibit 79.5% homology(Yang et al., 2020), and the clinical manifestations of the infections produced by either of these viruses have been found to have numerous similarities. The possible pharmacological effects of glycyrrhizin in the therapy of COVID-19 were investigated Gomaa and Abdel-Wadood (2021). The researchers discovered that glycyrrhizin has a number of therapeutic properties, including binding to the enzyme angiotensin-converting enzyme II (ACE2), downregulating proinflammatory cytokines, inducing endogenous interferon, inhibiting intracellular thrombin and R accumulation, and producing excessive amounts of exudates from the airways. According to these results, glycyrrhizin shows promise as a medication to treat COVID-19. It was discovered that glycyrrhizin lessened the pathogenic effects of SARS-CoV. Glycoprotein-blocked viruses can only spread by adsorption and penetration, which work well in pre and post the viral adsorption phases (Cinatl et al., 2003). A change in the entry's chemical composition that can both produce cytotoxicity and boost glycyrrhizin's potency and antiviral activity. Based on the docking data, glycyrrhizin may connect with ACE2 through binding citations (ARG-559, GLN-388, ARG-393, and ASP-30). The calculated ΔG (kcal / mol) of ACE2 is -9 (Murck, 2020). Glycyrrhizin's low toxicity implies that ACE2 might have antiviral effects on SARS. Consequently, it would be advantageous to look into ACE2's effectiveness in 2019 against nCoV infection (Chen and Du, 2020). In accordance with Zhang et al., 2017, the antiviral effect of apigenin can prevent the production of the virus's proteins by suppressing viral the translation process. This, in turn, affects the replication of enterovirus-71 (EV71) by interfering with the relationship of viral RNA with trans-acting variables regulating EV71 translation (Cao et al., 2022). This suggests that the inhibitory effect of celery to ACE results from a decline in the transformation of N-[3-(2-furyl) acryloyl]-L-phenylalanyl-glycyl-glycine by rabbit lung ACE in the absence of the seed of celery extract. Furthermore, recent studies have demonstrated that one of the primary ACE inhibitors is junipediol A 8-O-β-d-glucoside (Lima et al., 2015).

This is Huang Qin, one of *Scutellaria baicalensis*'s Chinese ingredients (Zhang et al., 2021). Baicalin is used in medicine for a variety of purposes, including as scavenging free radicals, reducing inflammation, and inhibiting apoptosis. Using the fetal rhesus kidney-4 (fRhK-4) cell line, several studies have discovered that baicalin suppresses the SARS coronavirus in vitro with an EC50 of (12.5 ug/ml at 48 hours and a selectivity index greater than 4 to 8). The current result noted baicalin may inhibit COVID-19 since the SARS virus and COVID-19 are related viruses. Additionally, Diomede et al. (2021)showed that baicalin may inhibit ACE in vitro with an IC50 value of 2.24 mM (Liao et al., 2020) figure 5.

Lin et al. (2024) noted that flavones baicalein and baicalin, which are glycosides present in *S. baicalensis*, demonstrated potent inhibitory effects on the hACE2 protein and the viral spike protein, respectively. Under ideal circumstances, baicalein-treated pseudovirus and baicalin-treated hACE2 were able to 98% suppress virus infection. In conclusion, we have determined which *S. baicalensis* compounds may serve as SARS-CoV-2 inhibitors and mediate the interaction between the hACE2 receptor and the Omicron spike protein. Future research is required to determine how baicalein and baicalin can be used therapeutically to treat SARS-CoV-2 variations. Hesperetin is 4'-methoxyy derivative as a flavanone, and hesperetin is its 4-methoxy derivative. Sweet oranges and lemons contain hesperidin, a flavanon-glycoside that is created naturally (Wang et al., 2022). Remarkably, hesperetin has been shown to modify the delayed inactivation phase of sodium current channel depolarization, and as a result, it may be utilized in LQT3 to produce innovative drugs that control fatal cardiac dys- arrhythmias (Diomede et al., 2021). (Parva et al., 2022) discovered that hesperidin inhibited the cell-free, dose-dependent, 3C-like SARS-coronavirus cleavage activity. Additionally, hesperetin's molecular docking to ACE2 has been demonstrated by specific aromas to support hesperidin's ability to block the enzyme. The findings imply that hesperetin may have an average ΔG (kcal/mol) of -8.3 when it comes to binding to ACE2 (Figure 6).

Conclusion

Herbal pharmaceutical medicines or the above-discussed active ingredients dramatically decreased morbidity and mortality infection rates in COVID-19 patients. Subsequent research is important in order to get a more profound comprehension of antiviral action mechanisms, as well as crucial pathways for viral entry and therapeutic interventions targeting COVID-19 pathogenesis. The best tool we have to control and prevent spread of infection in the community is prevention; the medical treatments available today are simply supportive. This study has indicated the role played by some

plants or their extracts in the ability to inhibit the enzymes responsible for the entry of the virus. This study was conducted and investigated through the molecular link between the active compounds in the extract and their interaction with the receptors, thus depriving the virus of the opportunity to enter the cells and start its viral cycle and cause the pathogenicity of the virus.

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Author contributions

Shurooq contributed in the idea and writing of the article, Aqeel helped participate in the drug docking program technique, Adnan was responsible for the article upload journal and correction, while the last Sadeeq researcher participated in interpreting the research results and comparing them with another research.

AI usage declaration

We did not use artificial intelligence in writing this research in any way.

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Conflict of interest

The author declares no conflict of interest. The manuscript has not been submitted for publication in other journal.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

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