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Original Research Article

In Silico Anti-Inflammation Prediction of Glycyrrhiza Extracts Against Covid-19

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Abstract

Due to its anti-inflammation effect, Glycyrrhiza extract is one of the natural extracts that may potentially combat coronavirus disease in 2019 (COVID-19). In the current article, we evaluate *in silico* (molecular docking) properties of active compounds available in Glycyrrhiza, native to Western Asia, North Africa, and Southern Europe, and compare its anti-inflammation effect with remdesivir as positive compounds based on molecular docking characteristics. The main active compounds were selected based on their significant roles in the pharmacological effects of Glycyrrhiza. The results obtained in this study demonstrated that most of the studied main compounds interacted stronger than selected remdesivir to inhibit the spike protein in COVID-19. The combined scores (binding affinity and drug-likeness properties of the ligand, demonstrated to be the potentially possible COVID-19 inhibitor compared with positive control. The active site analysis of the interactions also showed that Glycyrrhiza extract containing active compounds might have therapeutic effects against COVID-19.

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INTRODUCTION

COVID-19 pandemic has emerged to be an unexpected medical crisis worldwide. SARS-CoV-2 is investigated to have more infectious properties compared with MERS-CoV[1]. Its spread rate is very high worldwide. It has affected more than 239 million people worldwide until now[2]. World Health Organization (WHO) suggested the administration of remdesivir as an emergency medicine in a critical stage of infected patients[3].

Present SARS-CoV-2 virus is approximately 80% similar to SARS-CoV from the point of genome structure[4]. Coronavirus is a single-stranded RNA virus that is spherical. They have been characterized into four groups: alpha, beta, gamma, and delta types. Gamma and delta types of coronaviruses are host-dependent. However, alpha and beta types of the virus include human and local pathogens that are anticipated to be related to transmission in cross-species[5,6]. SARS-CoV and MERS-CoV are considered in the beta genus of coronavirus. They are related to a severe respiratory tract infection resulting in 10% and 35% of mortality rates[7,8].

The SARS-CoV target spike protein with PDB ID of 6M0J[9] is one of the targets that researchers are intended to discover small molecules to inhibit. It is one of the recognized targets that has attracted many researchers worldwide to predict using computer-aided drug discovery[10,11]. They aim to construct novel small molecules with the potential to suppress such protein targets in order to battle the COVID-19 virus[12].

The attention to plant extracts and extracted natural compounds in cosmetic formulations is rising. Natural products may significantly advance cosmetics performance since they have cosmetic and therapeutic-like belongings, known as cosmeceutical properties[13,14]. In the family of Leguminosae, the Glycyrrhiza genus includes more than 30 different

species, extensively spread worldwide. The most important clinical plant parts are rhizomes and roots, which are presently used in pharmaceutical manufacturing and the food industry[15]. A few years ago, the curiosity about potential plant activities in cosmetic formulations significantly increased. *Glycyrrhiza spp*. extracts are extensively employed in cosmetic products for their optimum whitening effects[16]. The pharmacological effects of Glycyrrhiza extracts are specifically referable to the incidence of specialized metabolites which belong to the class of flavonoids. Three main flavonoids are highlighted in glycyrrhiza: licochalcone A, glabridin, and dehydroglyasperin C[17,18]. Furthermore, licorice extract showed the best anti-inflammation effects compared with positive control drug in an *in vivo* model investigation in mice[19]. It is believed this study will help to evaluate the possible pharmacological effects of licorice's main flavonoids to inhibit the sets of amino acids needed for the interactions at the active pocket of target protein in SARS-CoV-2.

METHOD

Hardware and Software

The hardware and software used were the same as those reported by a previous study[20]. Python language was downloaded from www.python.com, Molecular Graphics Laboratory (MGL) tools software was downloaded from http://mgltools.scripps.edu, PyRx version 0.8 was downloaded from https://pyrx.sourceforge.io/, BIOVIA draw and Discovery studio visualizer 2017 were downloaded from http://accelrys.com.

Ligands

The identified structures of active flavonoids were downloaded from PubChem. Discovery studio visualizer was used to convert sdf format to PDB and further used for docking studies. The starting structures of the protein were prepared using AutoDock Tools. Water molecule was deleted, polar hydrogen and Kollman charges were added to the protein starting structure. The starting structure for all the ligands consisting of dehydroglyasperin C (PubChem CID 480775), glabridin (124052), licochalcone A (5318998), and remdesivir (121304016) was constructed using BIOVIA draw. Remdesivir was chosen as positive controls. Their structures were provided from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/). Gasteiger charges were assigned into optimized ligands using AutoDock Tools.

Receptors

Three-dimensional crystal structure of SARS-CoV-2 target Spike protein with PDB ID: 6M0J[9] was nominated and downloaded from Protein Data Bank (https://www.rcsb.org/) (**Figure 1**). The complexes bound to the receptor molecule, all the non-essential water molecules and heteroatoms were deleted, and ultimately hydrogen atoms were added to the receptor molecule using ArgusLab[21].

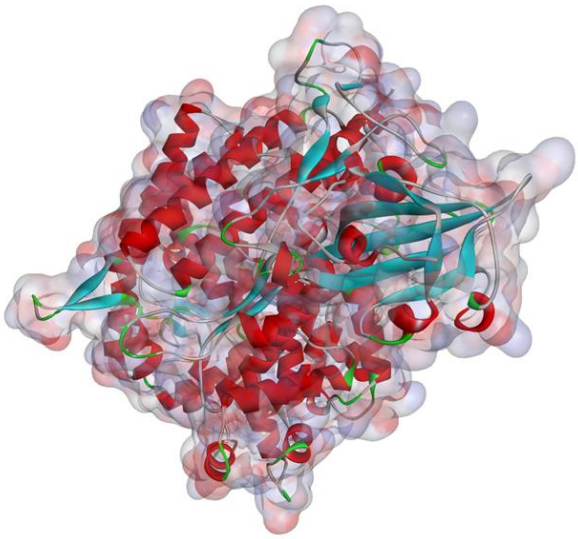

Figure 1. SARS-CoV-2 protein Spike with PDB ID: 6M0J.

Docking Protocol

The grid box was set with the size of 126 × 126 × 126 Å with the grid spacing of 0.375 Å at the binding site. One hundred fifty docking runs were conducted with a mutation rate of 0.02 and a crossover rate of 0.8. The population size was set to use 250 randomly placed individuals. Lamarckian genetic algorithm was used as the searching algorithm with a translational step of 0.2 Å, a quaternion step of 5 Å, and a torsion step of 5 Å[22].

Assessment

The parameters used in assessing and ranking the test ligands of the docking results were evidently stated.

RESULTS AND DISCUSSION

The docked conformation of spike protein, with the active conformation consisting of dehydroglyasperin

C, glabridin, licochalcone A, and remdesivir, clearly discovered numerous potential interactions were present. The docking results demonstrated dehydroglyasperin C with a free energy of binding (ΔG) of -8.3 kcal/mol after interaction with spike protein. It showed four hydrogen bonds with ASP367, ASN290, ILE291, and THR434; three alkyl bonds with PRO415, LYS441, and MET366; and one Pi-Pi T shaped bond with PHE438 (**Figure 2**).

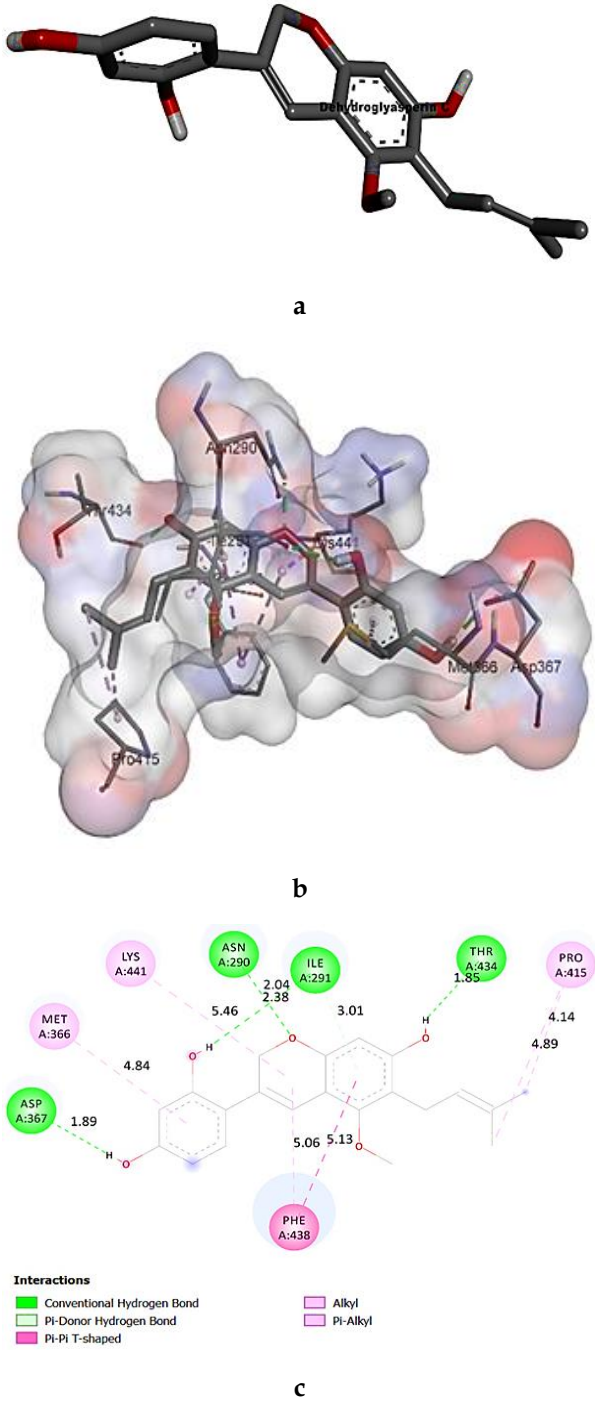

Figure 2. The 3D structure of the compound (**a**) and the 3D (**b**) and 2D (**c**) interactions between dehydroglyasperin C and the SARS-CoV-2 spike protein.

Glabridin, after interaction with spike protein, demonstrated four hydrogen bonds with GLU208, TYR196, GLN98, and ASN210, as well as five alkyl bonds with PRO565, VAL212, VAL209, LEU95, and LEU91 (**Figure 3**). It showed ΔG of -8.46 kcal/mol, the lowest among all the studied compounds compared with remdesivir.

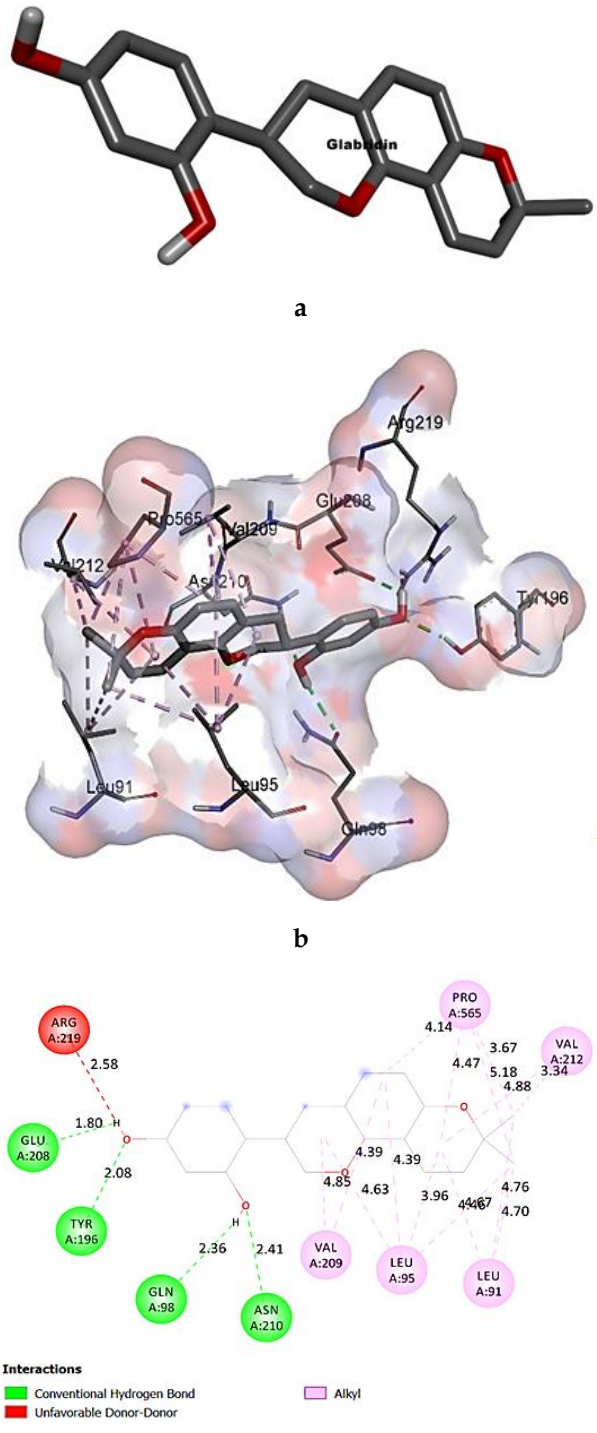

Figure 3. The 3D structure of the compound (**a**) and the 3D (**b**) and 2D (**c**) interactions between glabridin and the SARS-CoV-2 spike protein.

Licochalcone A demonstrated ΔG of -8.37 kcal/mol after interaction with spike protein. It showed conventional hydrogen bonds with ASP206, TRP566, and ASN210; pi sigma bond with LEU95; and three alkyl bonds with LEU91, VAL212, and PRO565 (**Figure 4**).

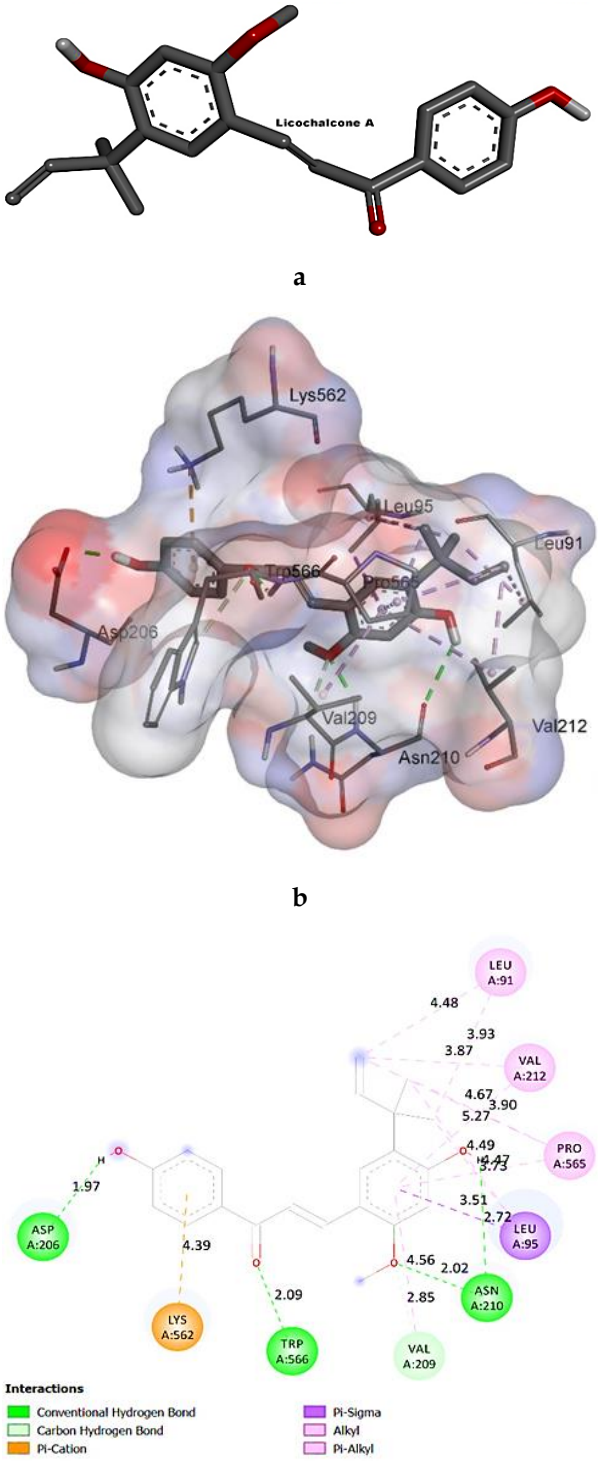

Figure 4. The 3D structure of the compound (**a**) and the 3D (**b**) and 2D (**c**) interactions between licochalcone A and the SARS-CoV-2 spike protein.

Remdesivir, as the second chosen standard approved recommended drug for COVID-19, showed three hydrogen bonds with ALA348, ASP382, and TYR385, as well as two alkyl bonds with LEU359 and VAL343 (**Figure 5**). Moreover, it showed ΔG of –5.97 kcal/mol.

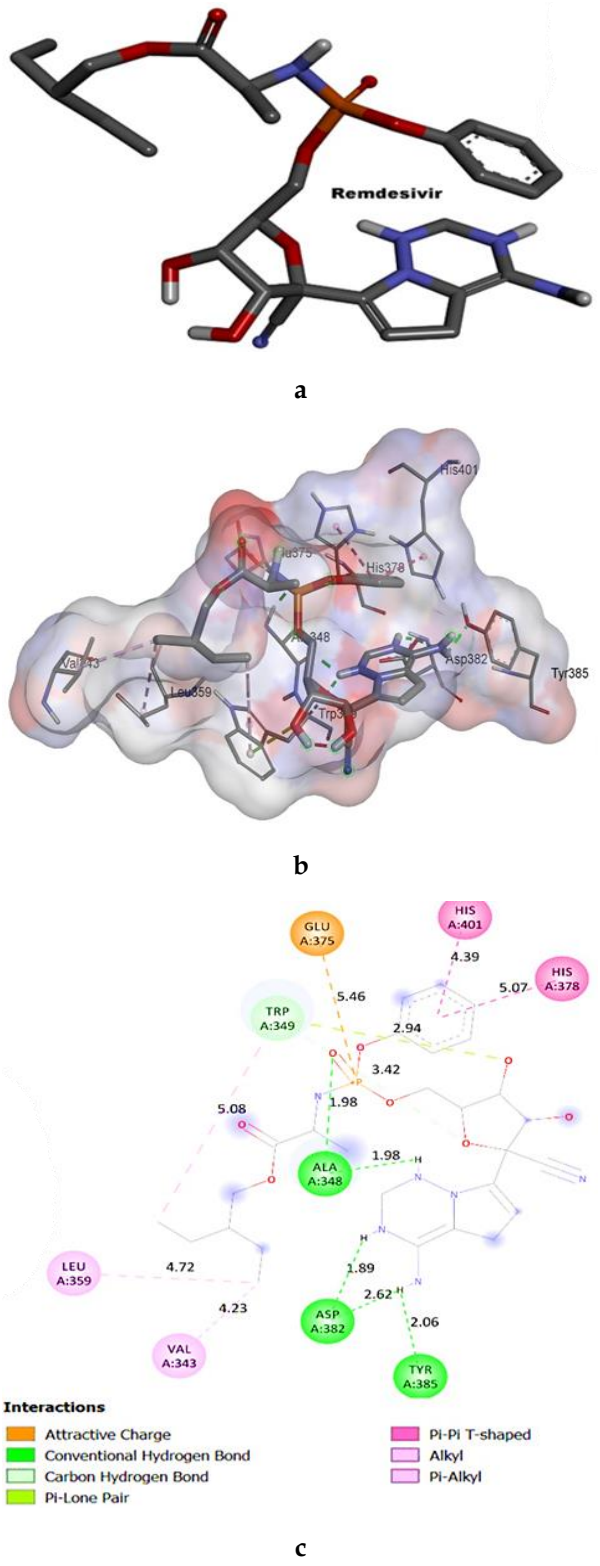

Figure 5. The 3D structure of the compound (**a**) and the 3D (**b**) and 2D (**c**) interactions between remdesivir and the SARS-CoV-2 spike protein.

The interaction between glabridin and spike protein with four hydrogen bonds showed the highest affinity among all other flavonoids and remdesivir as a positive control. However, dehydroglyasperin C showed four hydrogen bonds but demonstrated less affinity towards spike protein compared with licochalcone A. Licochalcone A formed a pi sigma bond in the protein's active pocket hyperconjugation, bending (tilting) of molecular structure[23]. It probably enhanced the ligand and receptor binding, and even though licochalcone A formed three hydrogen bonds but the whole affinity of the system towards studied protein was more than dehydroglyasperin C. Moreover, ASN210 in the structure of spike protein in interaction with licochalcone A is located in a way that caused two hydrogen bonds with the hydrogen of phenolic group and oxygen of ketonic group in the structure of licochalcone A. it causes a conjugation in the system and electrons can circulate in this conjugation results in a more stable system. This probably can explain the more stability and higher affinity of licochalcone A compared with dehydroglyasperin C in interaction with spike protein. The results of this study also confirm various previous *in silico* studies, which also identified metabolites from the genus Glycyrrhiza as inhibitors of the SARS-CoV-2 spike protein, complementing another study with the same plant against other targets such as the main protease of SARS-CoV-2.

CONCLUSION

Molecular docking assessment of the main identified flavonoids in Glycyrrhiza extract against spike protein of SARS-CoV-2 has been performed. All of the studied ligands' score binding affinity were better than the remdesivir (lower than -5.97 kcal/mol). However, based on the combined scores of binding affinities and the similarity of the ligands' drug profile, glabridin was the best potential inhibitor of the evaluated spike protein of the COVID-19 virus. Moreover, the active site analysis reveals that ASN210, PRO565, and LEU91 are among the most important amino acids due to their common occurrence in the ligand-protein interaction. Furthermore, since in Glycyrrhiza extract, surprisingly all the studied flavonoids are available so their synergistic effect may have more potential to inhibit spike protein of COVID-19 and may have more potential to be used for its treatment.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

FUNDING

None.

DATA AVAILABILITY

All the raw data on the results of research that the authors upload independently both on the open access repositories and other sources are available.

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None.

AUTHORS' CONTRIBUTIONS

Mansoureh Nazari: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review & editing.

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