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ORIGINAL ARTICLE

Anti-Inflammation Prediction of Orthosiphon Stamineus Extract Against Covid19 (In silico Study)

Mahdi Nazari V.[1], Masoumeh Nazari[1], Mansoureh Nazari V.[2]*

[1]Computer Engineering Department, Kooshiar High Tech Institute, Rasht, Guilan, Iran.
[2]School of Pharmacy, University August 17, 1945, Jakarta-14350, Indonesia.

ABSTRACT – *Orthosiphon stamineus Benth* (OS) due to its anti-inflammation effect is one of the possible options to fight the outbreak of coronavirus disease in 2019 (COVID-19). In this article, we evaluate *in silico* (molecular docking) properties of active compounds available in OS which is generally consumed by South east Asian people and compare its effect with remdesivir and favipiravir as positive compounds based on docking properties. The main active compounds were grouped based on their significant roles in OS. The results demonstrated that most of the studied main compounds perform better than selected drugs in inhibiting of the spike protein in COVID-19. The combined scores (in binding affinity, the drug-likeness properties of the ligand, revealed to be the best possible covid19 inhibitor compared to the other ligands. The active site analysis also demonstrated that OS active compounds might have a therapeutic effect against COVID19.

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Molecular docking
Anti-inflammation
COVID19

INTRODUCTION

SARS-CoV-2 (COVID-19) pandemic has caused an extraordinary medical crisis worldwide. SARS-CoV-2 is investigated to have more infectious properties compared with MERS-CoV [1]. Its spread rate is very high among countries. It has influenced more than 131 million people worldwide to date [2]. WHO suggested administering remdesivir and favipiravir as emergency medicine for critical stages of the infection with covid-19 [3]. The COVID-19 virus is almost 80% similar to SARS-CoV from the point of genome structure [4]. Coronavirus is a single-strand type of RNA virus that is spherical generally. They have been classified into four groups: alpha, beta, gamma, and also delta. Gamma and delta types of covid viruses are related to hosts.

In contrast, alpha and beta types include human and local pathogens which are expected to be linked to the occurrence of transmission in cross-species [5]. SARS-CoV and MERS-CoV are categorized in the beta genus of coronavirus. They are related to a severe respiratory tract infection that causes 10% and 35% of mortality rate, respectively [6]. Covid19 target spike with PDB ID of 6M0J is one of the targets that researchers are aimed to discover small molecules to inhibit it. This is one of the targets that has attracted medicinal chemists to predict using computer-aided drug discovery [7]. They try to develop novel small molecules which might suppress such targets in order to combat COVID-19 virus.

O*rthosiphon stamineus* Benth (OS) in the family of Lamiaceae is a well-known plant in conventional medicine. This herb grows in mild and tropical zones like India, Malaysia, China and Australia [8]. Chemical evaluation has expressed the availability of three types of chemical compounds in different types of OS extracts. The detected compounds include polymethoxylated flavonoids, phenylpropanoids and terpenoids. The most prominent flavonoids, isolated from the hydroalcoholic extract of OS leaves, include sinensetin (SIN), eupatorine (EUP), 3-hydroxy-5,6,7,4- tetramethoxyflavone (TMF) and caffeic acid derivatives, such as caffeic acid and rosmarinic acid (RA) [9]. Both anti-inflammatory and analgesic efficacies of standardized 50% methanol extract of OS was studied in rat and mouse models [10]. Furthermore, it demonstrated that oral administration of 1000 mg/kg of this extract was revealed to produce an anti-inflammatory effect [11]. Authors believe this study will help to estimate possible pharmacological effects of OS main compounds to inhibit the series of amino acids needed for the interactions at the active pocket of target protein in SARS-CoV-2.

MATERIALS AND METHODS

Protein preparation

Software

Python language was downloaded from www.python.com, Molecular graphics laboratory(MGL) tools software was downloaded from http://mgltools.scripps.edu and PyRx version 0.8 was downloaded from https://pyrx.sourceforge.io/, BIOVIA draw was downloaded from http://accelrys.com, Discovery studio visualizer 2017 downloaded from http://accelrys.com.

***CORRESPONDING AUTHOR** | Mansoureh Nazari V. | ✉ nazarimansoure@gmail.com

Methods

Three-dimensional crystal structure of covid19 target Spike with PDB ID: 6M0J, was selected and downloaded from Protein Data Bank (www.rvcsb.org/pdb) (Fig.1)[12]. 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 target receptor molecule using Argus Lab.

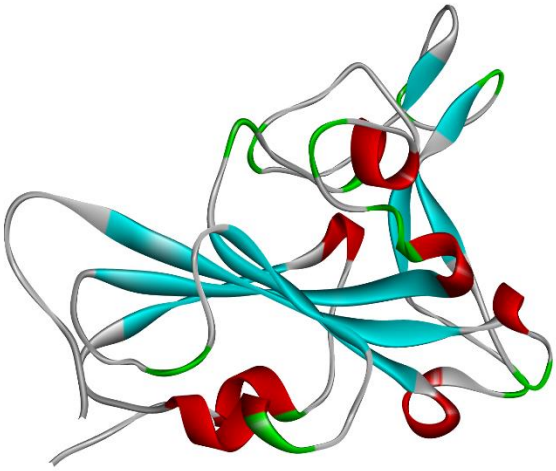


Figure 1. Protein Spike with PDB ID: 6M0J

Ligand preparation

The identified structures of active compounds were downloaded from Pubchem. Discovery studio visualizer was used to convert sdf format to PDB and further used for docking studies.

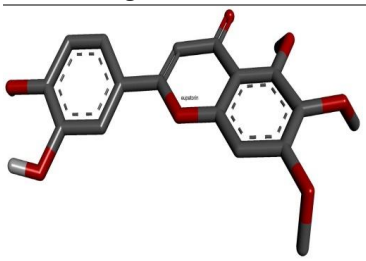
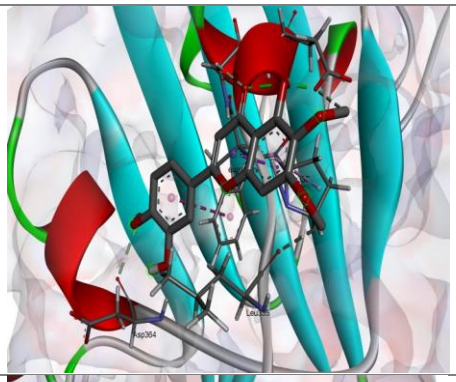
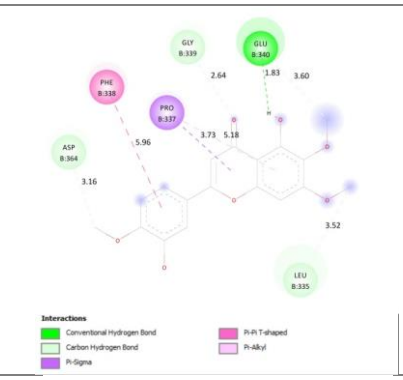
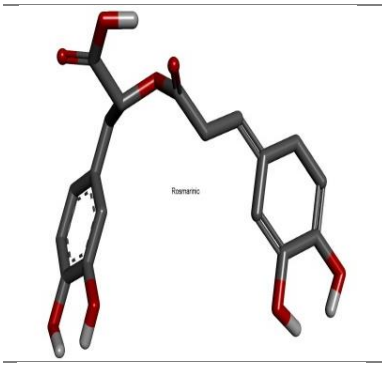
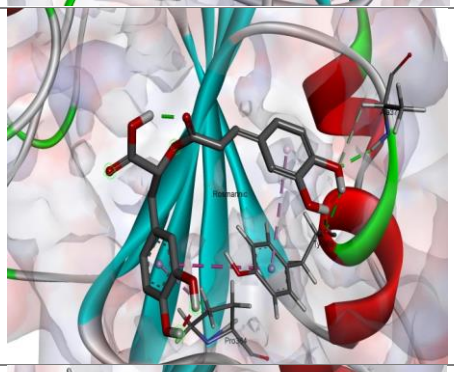
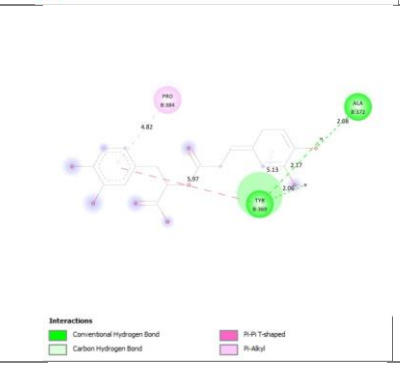
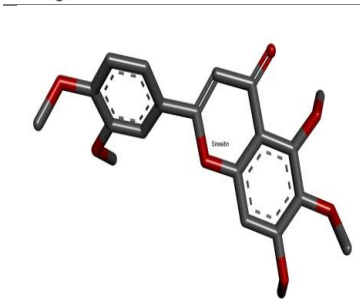
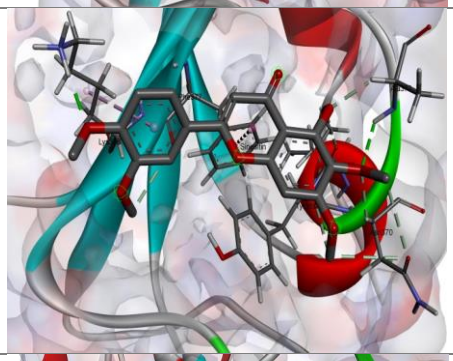
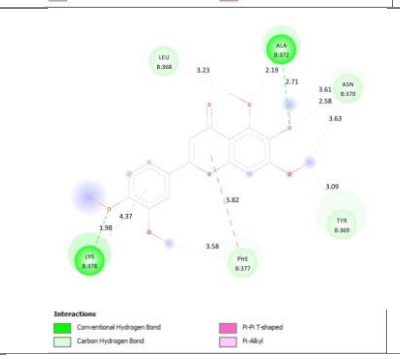
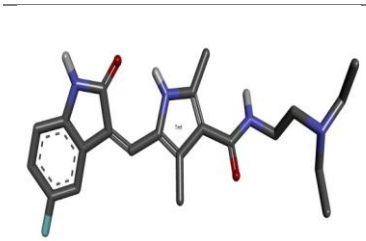
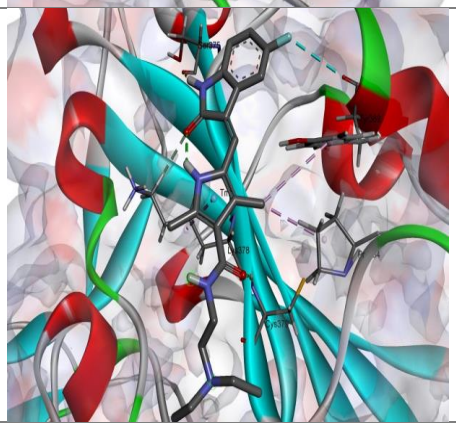
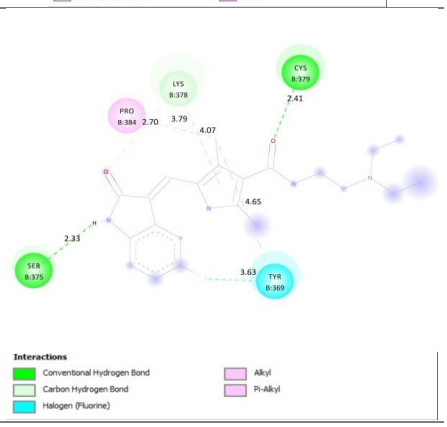
The starting structures of the protein was prepared using AutoDock tools. Water molecule was deleted, polar hydrogen and Kollman charges were added to the protein starting structure. The grid box was set with the size of 126×126×126 Å with the grid spacing of 0.375 Å at the binding site. The starting structure for all the ligands namely ra, sin, tmf and eup were constructed using BIOVIA draw. Favipiravir (FVP) and Remdesivir (RMD) were selected as positive controls. Their structures were provided from Pubchem website. Gasteiger charges were assigned into optimized ligands using Autodock Tools. 150 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. Most populated and lowest binding free energy.

RESULTS AND DISCUSSION

The docked conformation of SPIKE, with the active conformation of each ligand consists of TMF, SIN, RA, EUP, RMD and FVP clearly revealed that numerous potential interactions were present (Table 1).

Eupatorine with a free binding energy of -4.54 kcal/mol has shown one hydrogen bond with GLU340, Three carbon-hydrogen bonds with GLY339, ASP364 and LEU335, one pi-sigma bond with PRO337 one pi-pi-t-shaped bond with PHE338. Rosmarinic acid with free binding energy of -5.14 kcal/mol has shown two hydrogen bonds with ALA372 and TYR369, one pi-alkyl bond with PRO384. Sinensitin revealed two hydrogen bonds with ALA372 and LYS378 and four carbon-hydrogen bonds with PHE377, ASN370, LEU368 and TYR369. It showed the lowest free binding energy of -5.74 kcal/mol. 3'-hydroxy-5,6,7,4'-tetramethoxyflavone has shown two hydrogen bonds with SER375 and CYS379, one carbon-hydrogen bond with LYS378, one halogen bond with TYR369 and one alkyl bond with PRO384. It demonstrated the free binding energy of -4.69 kcal/mol. Favipiravir which was selected as a positive control has shown two hydrogen bonds with PRO384 and LEU387, one pi-pi-t stacked bond with TYR365 and also two pi-alkyl bonds with CYS432 and CYS379 with a free binding energy of -4.86 kcal/mol. Remdesivir as the second chosen standard approved recommended drug for covid19 showed three hydrogen bonds with THR345, ARG346 and ASN450, three carbon-hydrogen bonds with SER349, ASN354 and TYR351, three pi alkyl bonds with ALA344, ALA348 and ALA352. Moreover, it showed free binding energy of -1.84 kcal/mol. Based on the molecular docking results sinensitin has shown the highest affinity towards suppressing target protein in covid19 virus. The affinity of rosmarinic acid also is more than favipiravir. It suggests that the availability of four studied active compounds in OS extract may have a synergistic effect and cause a much stronger affinity towards inhibition of spike protein than remdesivir and favipiravir. However, this needs further study to be confirmed.

Table 1. The interactions between SPIKE and ligands.

Ligand structure	Interaction conformation1	Interaction conformation2
		
		
		
		

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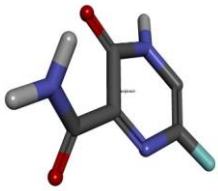	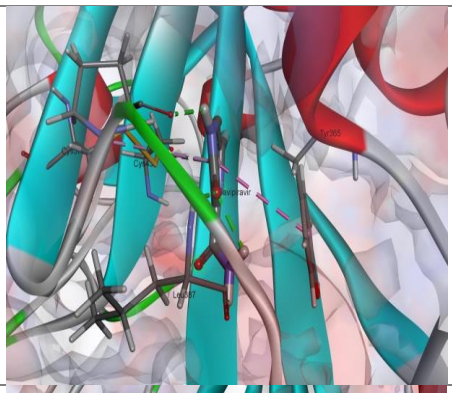	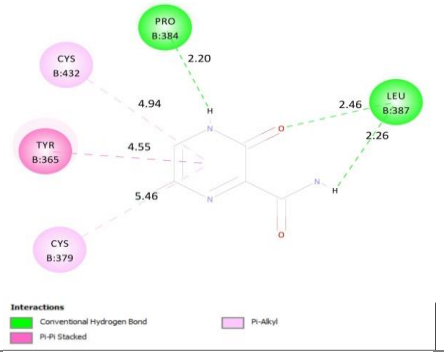
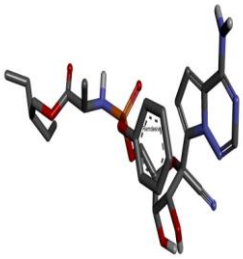	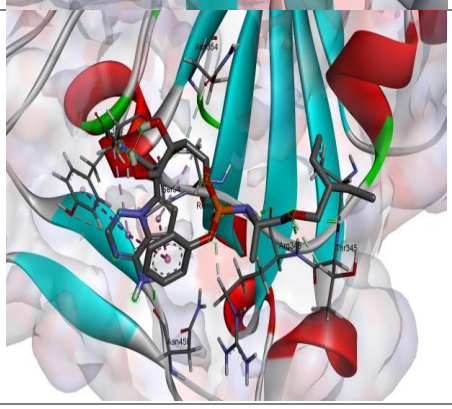	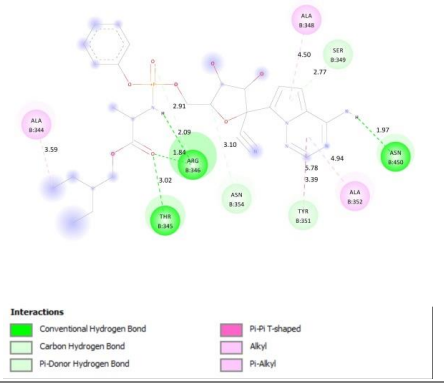

CONCLUSION

Molecular docking evaluation of the main identified active compounds in *orthosiphon stamineus* against COVID-19 spike target protein has been studied. All of the studied ligands score binding affinity were better than the remdesivir (lower than -1.84 kcal/mol). However, based on the combined scores of binding affinities and the similarity of drug profile of the ligands, sinensitin was found out to be the best possible inhibitor of the analyzed spike protein of SARS-CoV-2. Furthermore, the active site analysis also reveals that GLY384, TYR369 and PRO384 are among the most important amino acids due to their frequent incidence in the ligand-protein interaction. Moreover, since in OS extract naturally all the studied compounds are available so their synergistic effect may have more potential in inhibition of spike protein of covid19 and may have the potential for the treatment.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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